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SEARCH REQUEST FORM

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Requester's Full Name: _____ Examiner # :_____ Date: _____
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****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: _____

Inventors (please provide full names): _____

_____

Earliest Priority Filing Date: _____

***For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.**

Point of Contact:
[illegible]

****

STAFF USE ONLY	Type of Search		Vendors and cost where applicable	
Searcher: _____	NA Sequence (#)_____		STN _____	
Searcher Phone #: _____	AA Sequence (#)_____		Dialog _____	
Searcher Location: _____	Structure (#)	_____	Questel/Orbit _____	
Date Searcher Picked Up: _____	Bibliographic	_____	Dr.Link _____	
Date Completed: _____	Litigation	_____	Lexis/Nexis_____	
Searcher Prep & Review Time: _____	Fulltext	_____	Sequence Systems _____	
Clerical Prep Time: _____	Patent Family	_____	WWW/Internet _____	
Online Time: _____	Other	_____	Other (specify)_____	

590 (1-2000)

09/313,514

What is claimed is:

1. A method of treating a subject, comprising:
introducing into said subject a peritoneal dialysis fluid which includes an inhibitor of a PKC, thereby treating said subject.

2. The method of claim 1, wherein said inhibitor is a specific inhibitor of PKC.

3. The method of claim 2, wherein said inhibitor is selected from the group consisting of: an inhibitor of a PKC β, an inhibitor of PKC γ, and an inhibitor of PKC δ.

4. The method of claim 2, wherein said inhibitor is an inhibitor of PKC β.

5. The method of claim 4, wherein said inhibitor is an inhibitor of PKC β1.

6. The method of claim 4, wherein said inhibitor is a bis (indolyl) maleimide.

7. The method of claim 6, wherein said inhibitor is LY333531.

8. The method of claim 7, wherein said LY333531 is present in said dialysis fluid at about 1-1,000 nanometers.

9. The method of claim 1, wherein said dialysis fluid has a concentration of glucose of about 200nM.

10. The method of claim 1, wherein said subject has previously received peritoneal dialysis.

11. The method of claim 1, wherein said subject has been a peritoneal dialysis patient for at least 2 to 24 months.

12. The method of claim 1, wherein said subject has already developed permeability disjunction.

13. The method of claim 1, wherein said subject has not yet developed permeability disjunction.

14. The method of claim 1, wherein said subject is at risk for renal failure.

15. The method of claim 14, wherein said subject is in end-stage renal failure.

16. A peritoneal dialysis fluid comprising an inhibitor of a PKC.

17. The dialysis fluid of claim 16, wherein said inhibitor is a specific inhibitor of PKC.

18. The dialysis fluid of claim 17, wherein said inhibitor is an inhibitor of PKC β.

19. The dialysis fluid of claim 18, wherein said inhibitor is a bis (indolyl) maleimide.

20. The dialysis fluid of claim 19, wherein said inhibitor is LY333531.

21. The dialysis fluid of claim 20, wherein said LY333531 is present in said dialysis fluid at about 1-1,000 nanometers.

22. The dialysis fluid of claim 16, wherein said dialysis fluid has a concentration of glucose of about 200nM.

23. A method of making an improved peritoneal dialysis fluid, comprising:
providing a peritoneal dialysis fluid; and
adding to that fluid an inhibitor of a PKC, to thereby provide an improved dialysis fluid.

24. The method of claim 23, wherein said inhibitor is LY333531.

Bib Data Sheet

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
09/524,459	03/10/2000 RULE –	424	1615	10276-026001

APPLICANTS
George Liang King, Dover, MA ;

** CONTINUING DATA **********
THIS APPLN CLAIMS BENEFIT OF 60/124,043 03/12/1999

** FOREIGN APPLICATIONS **********

IF REQUIRED, FOREIGN FILING LICENSE GRANTED ** SMALL ENTITY **
** 05/17/2000

		STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
Foreign Priority claimed	☐ yes ☐ no	MA	3	24	3
35 USC 119 (a-d) conditions met	☐ yes ☐ no ☐ Met after Allowance				
Verified and Acknowledged	Examiner's Signature Initials				

ADDRESS

P Louis Myers
Fish & Richrdson P C
225 Franklin Street
Boston ,MA 02110-2804

TITLE

Inhibition of PKC to treat permability failure

FILING FEE RECEIVED	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit
446		

=> fil reg; d rn cn l11 1-6

FILE 'REGISTRY' ENTERED AT 10:21:53 ON 21 DEC 2000
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STRUCTURE FILE UPDATES: 20 DEC 2000 HIGHEST RN 310390-30-8
DICTIONARY FILE UPDATES: 20 DEC 2000 HIGHEST RN 310390-30-8

TSCA INFORMATION NOW CURRENT THROUGH July 8, 2000

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Structure search limits have been increased. See HELP SLIMIT for details.

L11 ANSWER 1 OF 6 REGISTRY COPYRIGHT 2000 ACS
RN 269390-35-4 REGISTRY
CN Kinase (phosphorylating), protein, C (Rat isoenzyme III) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN GenBank AF219629-derived protein GI 6942180
CN **Protein kinase C .delta. (Rattus isoenzyme III)**

L11 ANSWER 2 OF 6 REGISTRY COPYRIGHT 2000 ACS
RN 252903-42-7 REGISTRY
CN **Protein kinase C beta (PRKCB1) (human clone A-345G4 gene A-345G4 C-terminal fragment) (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN GenBank AC002302-derived protein GI 2695573

L11 ANSWER 3 OF 6 REGISTRY COPYRIGHT 2000 ACS
RN 221895-81-4 REGISTRY
CN Kinase (phosphorylating), protein, C (human clone A-113A6 gene PRKCB isoenzyme .beta.2 C-terminal fragment reduced) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN GenBank AC002299-derived protein GI 2822146
CN **Protein kinase C beta (human clone A-113A6 gene A-113A6.1 splice form-1 N-terminal fragment)**
CN Protein kinase C isoenzyme .beta.2 (human clone BAC A-113A6 gene PRKCB C-terminal fragment reduced)

L11 ANSWER 4 OF 6 REGISTRY COPYRIGHT 2000 ACS
RN 221895-79-0 REGISTRY
CN Kinase (phosphorylating), protein, C (human clone A-113A6 gene PRKCB isoenzyme .beta.1 C-terminal fragment reduced) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN GenBank AC002299-derived protein GI 2822147
CN **Protein kinase C beta (human clone A-113A6 gene A-113A6.2 splice form 2 N-terminal fragment)**
CN Protein kinase C isoenzyme .beta.1 (human clone BAC A-113A6 gene PRKCB C-terminal fragment reduced)

L11 ANSWER 5 OF 6 REGISTRY COPYRIGHT 2000 ACS
RN 147519-86-6 REGISTRY
CN Kinase (phosphorylating), protein, C (human clone NE-2 isoenzyme .theta. reduced) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN GenBank L07032-derived protein GI 558100
CN Kinase (phosphorylating), protein, C (human gene PRKCQ isoenzyme .theta. reduced)
CN **Protein kinase C .theta. (human gene PRKCQ reduced)**

CN Protein kinase C isoform .theta. (human clone NE-2)

L11 ANSWER 6 OF 6 REGISTRY COPYRIGHT 2000 ACS
RN 141436-78-4 REGISTRY
CN Kinase (phosphorylating), protein, C (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Calcium-dependent protein kinase C
CN Calcium/phospholipid-dependent protein kinase
CN Calcium/phospholipid-dependent protein kinase C
CN Phosphatidylserine-sensitive calcium-dependent protein kinase
CN **Protein kinase C**

=> d rn cn l9; d rn cn l10

L9 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2000 ACS
RN **541-59-3** REGISTRY
CN 1H-Pyrrole-2,5-dione (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Maleimide (6CI, 8CI)
OTHER NAMES:
CN 3-Pyrroline-2,5-dione
CN Maleic imide
CN Pyrrole-2,5-dione

L10 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2000 ACS
RN 169939-94-0 REGISTRY
CN 9H,18H-5,21:12,17-Dimethenodibenzo[e,k]pyrrolo[3,4-h][1,4,13]oxadiazacyclohexadecine-18,20(19H)-dione, 9-[(dimethylamino)methyl]-6,7,10,11-tetrahydro-, (9S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 9H,18H-5,21:12,17-Dimethenodibenzo[e,k]pyrrolo[3,4-h][1,4,13]oxadiazacyclohexadecine-18,20(19H)-dione, 9-[(dimethylamino)methyl]-6,7,10,11-tetrahydro-, (S)-
OTHER NAMES:
CN **LY 333531**

=> fil capl; d que 156; d que 169; s 156 or 169; fil medl; d que 138; d que 144; s 138 or 144

FILE 'CAPLUS' ENTERED AT 16:55:31 ON 21 DEC 2000
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FILE COVERS 1967 - 21 Dec 2000 VOL 133 ISS 26
FILE LAST UPDATED: 20 Dec 2000 (20001220/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

This file supports REG1stRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

Now you can extend your author, patent assignee, patent information, and title searches back to 1907. The records from 1907-1966 now have this searchable data in CAOLD. You now have electronic access to all of CA: 1907 to 1966 in CAOLD and 1967 to the present in CAPLUS on STN.

The CA Lexicon is now available in the Controlled Term (/CT) field.
Enter HELP LEXICON for full details.


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L45 (         1)SEA FILE=REGISTRY ABB=ON  "PROTEIN KINASE C"/CN
L46 (         3)SEA FILE=REGISTRY ABB=ON  ("PROTEIN KINASE C BETA (HUMAN CLONE
                  A-113A6 GENE A-113A6.1 SPLICE FORM-1 N-TERMINAL FRAGMENT)"/CN
                  OR "PROTEIN KINASE C BETA (HUMAN CLONE A-113A6 GENE A-113A6.2
                  SPLICE FORM 2 N-TERMINAL FRAGMENT)"/CN OR "PROTEIN KINASE C
                  BETA (PRKCB1) (HUMAN CLONE A-345G4 GENE A-345G4 C-TERMINAL
                  FRAGMENT)"/CN)
L47 (         2)SEA FILE=REGISTRY ABB=ON  "PROTEIN KINASE C .DELTA. (RATTUS
                  ISOENZYME III)"/CN OR "PROTEIN KINASE C .THETA. (HUMAN GENE
                  PRKCQ REDUCED)"/CN
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L50 (     32734)SEA FILE=CAPLUS ABB=ON  (L45 OR L46 OR L47) OR PROTEIN KINASE
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L51 (      1448)SEA FILE=CAPLUS ABB=ON  L48
L52 (       239)SEA FILE=CAPLUS ABB=ON  ?MALEIMIDE?(3A)?INDOL?
L53 (        65)SEA FILE=CAPLUS ABB=ON  L49 OR LY333531 OR LY-333531
L54 (     18433)SEA FILE=CAPLUS ABB=ON  L50(L)INHIBIT?
L55 (     14225)SEA FILE=CAPLUS ABB=ON  DIALY?/OBI
L56           4 SEA FILE=CAPLUS ABB=ON  (L54 OR (L51 OR L52 OR L53)) AND L55


L57 (     46468)SEA FILE=CAPLUS ABB=ON  DIALY?
L58 (         1)SEA FILE=REGISTRY ABB=ON  "PROTEIN KINASE C"/CN
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L59 (         3)SEA FILE=REGISTRY ABB=ON  ("PROTEIN KINASE C BETA (HUMAN CLONE
                A-113A6 GENE A-113A6.1 SPLICE FORM-1 N-TERMINAL FRAGMENT)"/CN
                OR "PROTEIN KINASE C BETA (HUMAN CLONE A-113A6 GENE A-113A6.2
                SPLICE FORM 2 N-TERMINAL FRAGMENT)"/CN OR "PROTEIN KINASE C
                BETA (PRKCB1) (HUMAN CLONE A-345G4 GENE A-345G4 C-TERMINAL
                FRAGMENT)"/CN)
L60 (         2)SEA FILE=REGISTRY ABB=ON  "PROTEIN KINASE C .DELTA. (RATTUS
                ISOENZYME III)"/CN OR "PROTEIN KINASE C .THETA. (HUMAN GENE
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L61 (         1)SEA FILE=REGISTRY ABB=ON  541-59-3
L62 (         1)SEA FILE=REGISTRY ABB=ON  "LY 333531"/CN
L63 (     32734)SEA FILE=CAPLUS ABB=ON  (L58 OR L59 OR L60) OR PROTEIN KINASE
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L64 (      1448)SEA FILE=CAPLUS ABB=ON  L61
L65 (       239)SEA FILE=CAPLUS ABB=ON  ?MALEIMIDE?(3A)?INDOL?
L66 (        65)SEA FILE=CAPLUS ABB=ON  L62 OR LY333531 OR LY 333531
L67 (     18433)SEA FILE=CAPLUS ABB=ON  L63(L)INHIBIT?
L68 (     23684)SEA FILE=CAPLUS ABB=ON  PERITONE?
L69           4 SEA FILE=CAPLUS ABB=ON  (L67 OR (L64 OR L65 OR L66)) AND L68
                AND L57


L70           6 L56 OR L69


FILE 'MEDLINE' ENTERED AT 16:55:32 ON 21 DEC 2000

 FILE LAST UPDATED: 27 OCT 2000 (20001027/UP).  FILE COVERS 1960 TO DATE.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2000 vocabulary.  Enter HELP THESAURUS for details.

 The OLDMEDLINE file segment now contains data from 1958 through 1965.
 Enter HELP CONTENT for details.

 Left, right, and simultaneous left and right truncation are available in the
 Basic Index.  See HELP SFIELDS for details.

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 COMPLETED.  NOTICE WILL BE GIVEN ONCE THE RELOAD IS COMPLETED AND
 RELOAD DETAILS WILL BE FOUND IN HELP RLOAD.


L34 (     20698)SEA FILE=MEDLINE ABB=ON  PROTEIN KINASE C/CT
L35 (      5782)SEA FILE=MEDLINE ABB=ON  L34(L)AI/CT - Subheading = antagonists &
L36 (     13296)SEA FILE=MEDLINE ABB=ON  PERITONEAL DIALYSIS+NT/CT                inhibitors
L37 (        28)SEA FILE=MEDLINE ABB=ON  LY333531 OR LY 333531
L38           0 SEA FILE=MEDLINE ABB=ON  (L35 OR L37) AND L36


L39 (     13296)SEA FILE=MEDLINE ABB=ON  PERITONEAL DIALYSIS+NT/CT
L40 (      6693)SEA FILE=MEDLINE ABB=ON  MALEIMIDES+NT/CT
L41 (    104913)SEA FILE=MEDLINE ABB=ON  INDOLES+NT/CT
L42 (      5003)SEA FILE=MEDLINE ABB=ON  L40(L)(AD OR PD OR TU)/CT  } Subheadings
L43 (     54621)SEA FILE=MEDLINE ABB=ON  L41(L)(AD OR PD OR TU)/CT  } AD - administration & dosage
L44          19 SEA FILE=MEDLINE ABB=ON  (L42 OR L43) AND L39          PD - pharmacology
                                                                       TU - therapeutic use


L71          19 L38 OR L44
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=> fil embase; d que l11; d que l15; s l11 or l15; fil biosis; d que l22; d que l28; s l22
or l28; fil wpids; d que l33

FILE 'EMBASE' ENTERED AT 16:56:06 ON 21 DEC 2000
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 FILE COVERS 1974 TO 14 Dec 2000 (20001214/ED)

 EMBASE has been reloaded. Enter HELP RLOAD for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


L2        11627 SEA FILE=EMBASE ABB=ON  DIALYSIS+NT/CT
L3           47 SEA FILE=EMBASE ABB=ON  LY333531 OR LY 333531
L4          173 SEA FILE=EMBASE ABB=ON  MALEIMIDE/CT
L5         8765 SEA FILE=EMBASE ABB=ON  ?MALEIMIDE?
L7          582 SEA FILE=EMBASE ABB=ON  INDOL?(3A)L5
L9          376 SEA FILE=EMBASE ABB=ON  BISINDOLYLMALEIMIDE/CT
L11           2 SEA FILE=EMBASE ABB=ON  L2 AND (L9 OR L4 OR L7 OR L3)



L1        20569 SEA FILE=EMBASE ABB=ON  PROTEIN KINASE C/CT
L2        11627 SEA FILE=EMBASE ABB=ON  DIALYSIS+NT/CT
L13       10282 SEA FILE=EMBASE ABB=ON  ENZYME INHIBITOR/CT
L14       53167 SEA FILE=EMBASE ABB=ON  ENZYME INHIBITION+NT/CT
L15           1 SEA FILE=EMBASE ABB=ON  L1 AND (L13 OR L14) AND L2



L72           3 L11 OR L15


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FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
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RECORDS LAST ADDED: 21 December 2000 (20001221/ED)

The BIOSIS file has been reloaded.  Enter HELP RLOAD and HELP REINDEXING
for details.


L16       56287 SEA FILE=BIOSIS ABB=ON  DIALY?
L17         594 SEA FILE=BIOSIS ABB=ON  BISINDOLYLMALEIMIDE#
L18          47 SEA FILE=BIOSIS ABB=ON  ?MALEIMIDE?(3A)INDOL?
L19          50 SEA FILE=BIOSIS ABB=ON  LY333531 OR LY 333531
L22           7 SEA FILE=BIOSIS ABB=ON  L16 AND ((L17 OR L18 OR L19))



L16       56287 SEA FILE=BIOSIS ABB=ON  DIALY?
L20       42872 SEA FILE=BIOSIS ABB=ON  PKC OR PROTEIN KINASE C
L21       11855 SEA FILE=BIOSIS ABB=ON  L20(5A)INHIBIT?
L27       50663 SEA FILE=BIOSIS ABB=ON  PERITONE?
L28           3 SEA FILE=BIOSIS ABB=ON  L21 AND L16 AND L27



L73          10 L22 OR L28
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>>>UPDATE WEEKS:
MOST RECENT DERWENT WEEK            200066   <200066/DW>
DERWENT WEEK FOR CHEMICAL CODING:   200066
DERWENT WEEK FOR POLYMER INDEXING:  200066
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

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L29         9881 SEA FILE=WPIDS ABB=ON  DIALY?
L30          450 SEA FILE=WPIDS ABB=ON  PKC OR PROTEIN KINASE C
L31            1 SEA FILE=WPIDS ABB=ON  LY333531 OR LY 333531
L32           36 SEA FILE=WPIDS ABB=ON  ?MALEIMIDE?(3A)INDOL? OR BISINDOLYLMALEI
                 MIDE#
L33            4 SEA FILE=WPIDS ABB=ON  L29 AND ((L30 OR L31 OR L32))



=> dup rem l71,l73,l70,l72,l33

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PROCESSING COMPLETED FOR L73
PROCESSING COMPLETED FOR L70
PROCESSING COMPLETED FOR L72
PROCESSING COMPLETED FOR L33
L74           39 DUP REM L71 L73 L70 L72 L33 (3 DUPLICATES REMOVED)
                 ANSWERS '1-19' FROM FILE MEDLINE
                 ANSWERS '20-29' FROM FILE BIOSIS
                 ANSWERS '30-33' FROM FILE CAPLUS
                 ANSWERS '34-36' FROM FILE EMBASE
                 ANSWERS '37-39' FROM FILE WPIDS

=> d ibib ab 1-39; fil home


L74  ANSWER 1 OF 39  MEDLINE
ACCESSION NUMBER:    97451391     MEDLINE
DOCUMENT NUMBER:     97451391
```

TITLE: Characterization of human erythrocyte choline transport in chronic renal failure.
AUTHOR: Riley S P; Talbot N J; Ahmed M J; Jouhal K; Hendry B M
CORPORATE SOURCE: Department of Medicine, King's College School of Medicine and Dentistry, London, UK.
SOURCE: NEPHROLOGY, DIALYSIS, TRANSPLANTATION, (1997 Sep) 12 (9) 1921-7.
Journal code: N7J. ISSN: 0931-0509.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
ENTRY WEEK: 19980104

AB BACKGROUND: Membrane transport of choline cations is elevated in renal failure in erythrocytes and cerebral tissue but the origins and clinical importance of this are unknown. METHODS: The membrane transport changes have been characterized using erythrocytes from patients on maintenance haemodialysis (HD), patients on continuous ambulatory peritoneal dialysis (CAPD), and control subjects. Data were obtained from cells depleted of intracellular choline to create zero-trans (ZT) conditions for choline influx. [14C]-choline influx measurements provided a kinetic description of choline flux as the sum of a saturable transport system (defined by Vmax and Km) and an apparent diffusion pathway. Inhibition of choline transport by hemicholinium-3 (HC-3), quinine and N-ethylmaleimide (NEM) has been studied. Actions of three cationic polyamine putative uraemic toxins (putrescine, spermidine, spermine) were tested in control erythrocytes. RESULTS: Mean (SEM) Vmax (ZT) was increased in HD at 45.0 (3.0) mumol/l cells/h and in CAPD at 46.6 (2.5) mumol/l cells/h compared to controls (30.0 (2.0) mumol/l cells/h). Mean Km (ZT) was not significantly altered in HD or CAPD (HD: 6.1 (1.6) microM; CAPD: 5.5 (0.7) microM; control: 5.1 (0.9) microM). The sensitivity of choline transport to the inhibitors tested was not altered in HD. 1.0 mM quinine, 2.0 mM NEM and 1.0 mM HC-3 caused 75-90% inhibition of transport in both HD and controls. For inhibition of ZT influx of 25 microM choline the mean IC50 of quinine was 90 (9) microM in HD and 101 (13) microM in controls (n.s.). The ZT influx of 200 microM choline was not altered by any of the polyamines at concentrations up to 1.0 mM. CONCLUSIONS: Membrane choline transport in CRF remains protein-mediated and exhibits normal substrate and inhibitor affinities; high values of Vmax seem to occur through increased surface expression of an active normal choline transporter. Increases in plasma polyamines cannot explain the choline transport changes in CRF.

L74 ANSWER 2 OF 39 MEDLINE
ACCESSION NUMBER: 1998256920 MEDLINE
DOCUMENT NUMBER: 98256920
TITLE: [Intraperitoneal administration of drugs in patients treated with peritoneal dialysis].
Dootrzewnowe podawanie lekow u chorych leczonych dializa otrzewnowa.
AUTHOR: Grzegorzewska A E
CORPORATE SOURCE: Klinika Nefrologii Instytutu Chorob Wewnetrznych Akademii Medycznej im. Karola Marcinkowskiego w Poznaniu.
SOURCE: POLSKIE ARCHIWUM MEDYCYNY WEWNETRZNEJ, (1997 Nov) 98 (11) 452-8. Ref: 60
Journal code: PAV. ISSN: 0032-3772.
PUB. COUNTRY: Poland
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: Polish
ENTRY MONTH: 199808
ENTRY WEEK: 19980803

L74 ANSWER 3 OF 39 MEDLINE

ACCESSION NUMBER: 95363324 MEDLINE
DOCUMENT NUMBER: 95363324
TITLE: Effects of intraperitoneal cyclooxygenase inhibition on inflammatory mediators in dialysate and peritoneal membrane characteristics during peritonitis in continuous ambulatory peritoneal dialysis.
AUTHOR: Zemel D; Struijk D G; Dinkla C; Stolk L M; ten Berge I J; Krediet R T
CORPORATE SOURCE: Department of Pharmacy, Academic Medical Center, Amsterdam, The Netherlands..
SOURCE: JOURNAL OF LABORATORY AND CLINICAL MEDICINE, (1995 Aug) 126 (2) 204-15.
Journal code: IVR. ISSN: 0022-2143.
PUB. COUNTRY: United States
(CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199511

AB Peritonitis complicating continuous ambulatory peritoneal dialysis (CAPD) can be used as an in vivo model to study the contribution of mediators in dialysate to the regulation of peritoneal permeability. Previously we reported that changes in the peritoneal appearance rates of the cytokines interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF alpha) were related to alterations in the effective peritoneal surface area. Changes in the intrinsic peritoneal permeability were mainly related to those in the peritoneal appearance rate of the prostanoid prostaglandin E2 (PGE2) and partly also to that of IL-6. In this intervention study the role of these mediators was further analyzed. Eleven peritonitis episodes were followed on 8 consecutive days from the start of the infection and once after recovery. Indomethacin was given intraperitoneally during the first 3 days. beta 2-Microglobulin clearance was used as indicator of the effective peritoneal surface area. The intrinsic peritoneal permeability was characterized functionally by the restriction coefficient. The 15 peritonitis episodes studied previously served as the control group. This study supports the formerly obtained relationships in two ways. First, significant reductions were observed for peritoneal PGE2, 6-keto-PGF1 alpha, and TxB2 during cyclooxygenase inhibition to 6%, 0.6%, and 9% of the values on day 1, whereas simultaneously the intrinsic permeability was less increased. This indomethacin effect on intrinsic permeability was not entirely significant, probably because of the additional role of IL-6, which was not influenced by indomethacin. Also, the appearance rate of TNF alpha in the effluent was not affected by cyclooxygenase inhibition. Accordingly, the changes in the effective surface area were similar to those in the control group. Second, in 8 of the 11 cases, new rises both in peritoneal PGE2 and in intrinsic permeability occurred after discontinuation of indomethacin. Rebounds were not seen for TNF alpha or IL-6, and, consistently, not for the effective surface area. In conclusion, local cyclooxygenase inhibition results in a less-increased intrinsic permeability during peritonitis but has no effect on the effective surface area. These data support our previous finding that IL-6 and TNF alpha contribute to alterations in surface area, whereas PGE2 is more involved in intrinsic peritoneal permeability changes.

L74 ANSWER 4 OF 39 MEDLINE
ACCESSION NUMBER: 94002465 MEDLINE
DOCUMENT NUMBER: 94002465
TITLE: Learning peritoneal physiology by pharmacological manipulation.
AUTHOR: Maher J F; Hirszel P
CORPORATE SOURCE: Department of Medicine, Uniformed Services University of the Health Sciences, Bethesda, Maryland 20814-4799..
SOURCE: PERITONEAL DIALYSIS INTERNATIONAL, (1993) 13 Suppl 2 S27-30.
Journal code: A2I. ISSN: 0896-8608.

PUB. COUNTRY: Canada
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199401

L74 ANSWER 5 OF 39 MEDLINE
ACCESSION NUMBER: 92192693 MEDLINE
DOCUMENT NUMBER: 92192693
TITLE: Prostaglandin E2 inhibits the release of tumor necrosis factor-alpha, rather than interleukin 1 beta, from human macrophages.
AUTHOR: Fieren M W; van den Bemd G J; Ben-Efraim S; Bonta I L
CORPORATE SOURCE: Department of Internal Medicine I, University Hospital Dijkzigt, Erasmus University, Rotterdam, The Netherlands..
SOURCE: IMMUNOLOGY LETTERS, (1992 Jan) 31 (1) 85-90.
Journal code: GIH. ISSN: 0165-2478.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199206

AB We have reported previously that macrophages obtained from renal patients on continuous ambulatory peritoneal dialysis (CAPD) during an episode of infectious peritonitis display a decrease in intracellular cAMP levels and in spontaneous in vitro release of PGE2 and PGI2. Such macrophages also release large quantities of IL-1 beta and TNF alpha when stimulated in vitro by LPS. In view of the interregulatory effects between PGE2 and macrophage cytokines (IL-1 beta and TNF alpha) in their production, we examined in the present work to what extent the LPS-induced release of either IL-1 beta or TNF alpha in vitro from CAPD-originated peritoneal macrophages is affected by graded doses of exogenous PGE2 (range 0-1000 ng/ml) and by the cyclooxygenase inhibitor indomethacin (INDO) (10(-6) M). IL-1 beta and TNF alpha were determined using an enzyme-linked immunoabsorbent assay and an immunoradiometric assay, respectively. We found that PGE2 invariably induced a dose-dependent decrease in TNF alpha release. In peritoneal macrophages collected during an infection-free period, TNF alpha release decreased from 3225 pg/ml (controls) to 353 pg/ml at 1000 ng/ml of PGE2, and in peritoneal macrophages collected during an episode of infectious peritonitis, it decreased from 4100 pg/ml (controls) to 545 pg/ml at 100 ng/ml of PGE2. However, PGE2 failed to influence the secretion of IL-1 beta. INDO induced an approx. two-fold increase in TNF alpha release, but had no effect on IL-1 beta release. These findings indicate that exogenous and endogenous PGE2 controls the release of TNF alpha rather than IL-1 beta from LPS-stimulated peritoneal macrophages.

L74 ANSWER 6 OF 39 MEDLINE
ACCESSION NUMBER: 91295452 MEDLINE
DOCUMENT NUMBER: 91295452
TITLE: Metabolism of 25-OH vitamin D3 by peritoneal macrophages from CAPD patients.
AUTHOR: Shany S; Rapoport J; Zuili I; Gavriel A; Lavi N; Chaimovitz C
CORPORATE SOURCE: Toor Institute, Soroka Medical Center, Beersheva, Israel..
SOURCE: KIDNEY INTERNATIONAL, (1991 May) 39 (5) 1005-11.
Journal code: KVB. ISSN: 0085-2538.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199110

AB The active metabolite of vitamin D, 1,25-dihydroxycholecalciferol (1,25(OH)2D3), is produced mainly by the kidney, but there is evidence for extrarenal production in certain circumstances. We studied whether peritoneal macrophages (PM) from CAPD patients were capable of

metabolizing 25-OH-D3 to 1,25(OH)2D3. We found that PM were able to metabolize 25-OH-D3 in vitro; the main product following 16 hours of incubation was 19-nor, 10-oxo, 25-OH-D3 with smaller amounts of 1,25(OH)2D3. However, after shorter incubations of three and five hours a larger portion of 1,25(OH)2D3 was produced. The metabolism of 25-OH-D3 was greatly enhanced in PM harvested during episodes of peritonitis. This property was specific for PM of CAPD patients, and was not found in PM from normal subjects. However, incubation of control PM with peritoneal effluent from CAPD patients resulted in induction of the ability of these cells to metabolize 25-OH-D3. This induction was enhanced by preincubation with peritoneal effluent from CAPD patients suffering from peritonitis. Prostaglandin E2 was found to be involved in this synthesis: addition of PGE2 to normal PM induced metabolism of 25-OH-D3, and incubation of PM from CAPD patients with indomethacin decreased the metabolism of 25-OH-D3. The vitamin D metabolites produced by PM from CAPD patients could have a role in immunological resistance to peritoneal infections.

L74 ANSWER 7 OF 39 MEDLINE
ACCESSION NUMBER: 90265013 MEDLINE
DOCUMENT NUMBER: 90265013
TITLE: Diversity in peritoneal macrophage response of CAPD patients to 1,25-dihydroxyvitamin D3.
AUTHOR: Levy R; Klein J; Rubinek T; Alkan M; Shany S; Chaimovitz C
CORPORATE SOURCE: Department of Urology, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel..
SOURCE: KIDNEY INTERNATIONAL, (1990 May) 37 (5) 1310-5.
Journal code: KVB. ISSN: 0085-2538.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199009
AB A major complication of continuous ambulatory peritoneal dialysis (CAPD) is peritonitis. Increasing the activity of the peritoneal macrophages, the predominant cell type found in the peritoneal cavity, may be a promising treatment for this infection. The effect of 1,25-dihydroxy-vitamin D3 [1,25(OH)2D3] on the activity of peritoneal macrophages from CAPD patients and nonuremic controls was studied. 1,25(OH)2D3 had a biphasic effect on superoxide generation in the concentration range of 2.5 10(-9) M to 5 x 10(-6) M with a peak at 2 x 10(-8) M. The addition of 2 x 10(-8) M 1,25(OH)2D3 to nonuremic control macrophages for 24 hours caused a significant twofold increase in superoxide generation in response to phorbol myristate acetate (PMA), from 2.21 + 0.2 to 4.1 + 0.2 nmol/10(6) mac (P less than 0.001), and enhanced the bactericidal activity from 60 + 7% to 85 + 9% (P less than 0.005). CAPD patients were divided into two groups: Group A, patients with high peritonitis incidence (HPI); group B, patients with low peritonitis incidence (LPI). Macrophages from HPI patients show a lower bactericidal activity (37 +/- 5%) and were not affected by 1,25(OH)2D3 after 24 hours of treatment. The increase in macrophage activity was seen only after three days of incubation with the hormone. Macrophages from this group generated a high amount of prostaglandin E2 (PGE2) during the first 24 hours in culture (7.8 +/- 0.52 ng/ml as compared with 0.35 +/- 0.03 ng/ml in the controls).(ABSTRACT TRUNCATED AT 250 WORDS)

L74 ANSWER 8 OF 39 MEDLINE
ACCESSION NUMBER: 87258006 MEDLINE
DOCUMENT NUMBER: 87258006
TITLE: Detection of Trp-P-1 and Trp-P-2, carcinogenic tryptophan pyrolysis products, in dialysis fluid of patients with uremia.
AUTHOR: Manabe S; Yanagisawa H; Guo S B; Abe S; Ishikawa S; Wada O
SOURCE: MUTATION RESEARCH, (1987 Jul) 179 (1) 33-40.
Journal code: NNA. ISSN: 0027-5107.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 198710
AB In order to estimate the exposure levels of mutagenic and carcinogenic heterocyclic amines in humans, we developed a high-performance liquid chromatography method to detect 3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole (Trp-P-1) and 3-amino-1-methyl-5H-pyrido[4,3-b]indole (Trp-P-2) in dialysis fluid of patients with uremia. Using this methods, dialysis fluid of 12 patients who had received hemodialysis treatment or continuous ambulatory peritoneal dialysis was examined. Trp-P-1 was detected in dialysate of all uremic patients (727 +/- 282 pmoles, n = 12). In patients who had been treated with continuous ambulatory peritoneal dialysis, the average amount of Trp-P-1 found in whole dialysate (6 l) per day was 710 +/- 203 pmoles (mean +/- S.D., n = 8). Moreover, Trp-P-2 could be detected in 5 out of 12 patients (206 +/- 85 pmoles, n = 5). These results indicate that patients with uremia are actually exposed to carcinogenic tryptophan pyrolysis products. The average exposure level of Trp-P-1 in uremic patients apparently exceeded 710 pmoles (150 ng) per day.

L74 ANSWER 9 OF 39 MEDLINE
ACCESSION NUMBER: 86207990 MEDLINE
DOCUMENT NUMBER: 86207990
TITLE: Human peritoneal eosinophils and formation of arachidonate cyclooxygenase products.
AUTHOR: Foegh M L; Maddox Y T; Ramwell P W
CONTRACT NUMBER: HL 32319 (NHLBI)
SOURCE: SCANDINAVIAN JOURNAL OF IMMUNOLOGY, (1986 May) 23 (5) 599-603.
Journal code: UCW. ISSN: 0300-9475.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 198608
AB Human peritoneal eosinophils were obtained from the waste dialysis bags of patients undergoing continuous ambulatory peritoneal dialysis. The number of eosinophils obtained from each bag varied from 3 X 10(7) to 288 X 10(7). The cells were incubated for 1 h in tissue culture medium and prostaglandin E2 (PGE2), 6-keto-prostaglandin F1 (6-keto-PGF1), and thromboxane B2 (TXB2) were determined by radioimmunoassay of the supernatant. The basal release as well as the stimulated release from the purified eosinophils of TXB2 were five times greater than the release of PGE2 and thirty times greater than the release of 6-keto-PGF1. A dose-response curve was achieved for all three cyclooxygenase products with the calcium ionophore A23187. The release of TXB2 was inhibited in a dose-dependent manner by the specific thromboxane A2 (TXA2) synthase inhibitor OKY-1581 and a corresponding increase in PGE2 and 6-keto-PGF1 was obtained. Indomethacin (5.6 X 10(-6) M) inhibited the cyclooxygenase products to almost undetectable levels.

L74 ANSWER 10 OF 39 MEDLINE
ACCESSION NUMBER: 86201303 MEDLINE
DOCUMENT NUMBER: 86201303
TITLE: Prostaglandin-mediated loss of proteins during peritonitis in continuous ambulatory peritoneal dialysis.
AUTHOR: Steinhauer H B; Schollmeyer P.
SOURCE: KIDNEY INTERNATIONAL, (1986 Feb) 29 (2) 584-90.
Journal code: KVB. ISSN: 0085-2538.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198608
AB The loss of proteins into the dialysate and the peritoneal generation of the immunoreactive prostanoids PGE2, 6-keto-PGF1 alpha, PGF2 alpha, and TXB2 were studied in 12 patients undergoing continuous ambulatory

peritoneal dialysis (CAPD) during 16 episodes of peritonitis and in inflammation-free periods. Protein permeability, defined as the ratio of dialysate/plasma protein (D/P), decreased with increasing molecular weight, independent of the condition of the peritoneum. With peritonitis a general rise of permeability was noticed for total protein (TP) and the individual proteins beta 2-microglobulin (beta MG), albumin (Alb), immunoglobulin G (IgG), and alpha 2-macroglobulin (alpha MG) (P less than 0.001). Simultaneously, an increase of dialysate prostanoids occurred with predominance of the vasodilative acting prostaglandins PGI2, determined as its metabolite 6-keto-PGF1 alpha, and PGE2 by factors of 8.4 and 9.7, respectively (P less than 0.001), in comparison to peritonitis-free control. In the early phase of peritonitis (0 to 12 hr after the onset of therapy) the augumented peritoneal prostaglandin synthesis correlated positively with the increased permeability of TP (r greater than or equal to 0.7446, P less than 0.01) and the individual proteins beta MG, Alb, IgG, and alpha MG (r greater than or equal to 0.5970, P less than 0.05). Inhibition of cyclo-oxigenase activity by local administration of indomethacin inhibited both the generation of 6-keto-PGF1 alpha and PGE2 by 39 and 42%, respectively (P less than 0.05), and the peritoneal loss of TP by 34% (P less than 0.05). In the absence of peritonitis indomethacin only diminished the synthesis of PGE2 whereas the generation of the other prostanoids remained unchanged.(ABSTRACT TRUNCATED AT 250 WORDS)

L74 ANSWER 11 OF 39 MEDLINE
ACCESSION NUMBER: 86048227 MEDLINE
DOCUMENT NUMBER: 86048227
TITLE: Comparison of methods for measurement of interstitial fluid pressure in cat skin/subcutis and muscle.
AUTHOR: Wiig H
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, ~~(1985 Nov) 249~~ (5 Pt 2) H929-44.
Journal code: 3U8. ISSN: 0002-9513.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198602
AB Interstitial fluid pressure (IFP) in cats was measured with four techniques, i.e., hollow perforated and porous polyethylene capsules, wick in needle (WIN), and micropipettes. During control conditions, skin IFP of -1.5 +/- 0.4 (SD) mmHg (n = 53) was obtained with micropipettes, whereas pressures recorded in subcutis with perforated and porous capsules were -1.6 +/- 0.9 (n = 26) and -1.6 +/- 0.8 mmHg (n = 13), respectively. These were all significantly different from the -1.2 +/- 0.5 mmHg (n = 50) obtained in subcutis with WIN. In skeletal muscle, control IFP of -0.5, -0.5, and -1.1 mmHg was measured with micropipettes, WIN, and porous capsules, respectively. During peritoneal dialysis skin and muscle IFP recorded with micropipettes and WIN was reduced by 3-3.5 mmHg, whereas pressure in porous and perforated capsules fell by 7 and 10 mmHg, respectively. Intravenous Ringer infusion caused a marked transient rise in capsular pressures, not reflected by micropipettes and WIN, but similar pressures were obtained 210 min after infusion. In conclusion, all techniques reflect true IFP under steady-state conditions. Both capsules apparently act like osmometers in acute overhydration or dehydration and are, in addition, sensitive to pressure changes in local veins and are therefore not suitable for measurement of changes in IFP that take place in less than a few hours.

L74 ANSWER 12 OF 39 MEDLINE
ACCESSION NUMBER: 85186262 MEDLINE
DOCUMENT NUMBER: 85186262
TITLE: Peritoneal permeability in the rat: modulation by microfilament-active agents.
AUTHOR: Alavi N; Lianos E; Van Liew J B; Mookerjee B K; Bentzel C J
SOURCE: KIDNEY INTERNATIONAL, (1985 Feb) 27 (2) 411-9.
Journal code: KVB. ISSN: 0085-2538.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198508

AB A model of peritoneal dialysis in the rat was used to determine the effects of cytochalasins on ultrastructure and peritoneal permeability to molecules of varying molecular weight. The permeability to urea, inulin, and plasma albumin were determined after intraperitoneal administration of cytochalasin B (2 to 10 X 10(-6) M) and cytochalasins D and E (2 X 10(-6) M). Cytochalasin B (20 X 10(-6) M) increased the permeability to inulin, urea, and albumin by 30, 60, and 150%, respectively. These effects were, to a large degree, reversible. Cytochalasins D and E produced greater increments in permeability for all molecules; this increase was only partially reversible. Ultrastructure analysis by scanning electron microscopy revealed extensive development of membrane protuberances (zeiotic knobs) on mesothelial cells exposed to cytochalasin B. A return to a normal apical cell surface was apparent although incomplete at 24 hr. Tight junctions were not grossly altered and major changes in intramembranous junctional strands were not observed. The major effect of cytochalasins on the cell surface may be responsible for the increased permeability to urea, predominately a transcellular probe. Inulin, which follows a paracellular route, was less affected. Altered protein permeability may be due to the action of cytochalasin on the exposed capillary endothelium in subdiaphragmatic areas where the mesothelium is discontinuous.

L74 ANSWER 13 OF 39 MEDLINE
ACCESSION NUMBER: 85301682 MEDLINE
DOCUMENT NUMBER: 85301682
TITLE: Acceleration of peritoneal solute transport by cytochalasin D.
AUTHOR: Hirszel P; Dodge K; Maher J F
SOURCE: UREMIA INVESTIGATION, (1984-85) 8 (2) 85-8.
Journal code: W9C. ISSN: 0740-1353.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198512

AB Because cytochalasin D affects intercellular junctions the effect of this agent on peritoneal transport was investigated in normal rabbits. Using commercially available dialysis solution, short-term control peritoneal dialyses were compared in the same animals to dialyses in which cytochalasin D was added intraperitoneally. A dose (325-920 micrograms/kg) dependent increase in peritoneal clearances of urea (49% increment at high dose) and of creatinine (67% increment) occurred when cytochalasin D was added. When solute transport was highest at the maximal dose, osmotically induced ultrafiltration decreased significantly to 33% of control values. Cytochalasin D induces aberrations in solute transport that resemble those accompanying and occasionally following peritonitis.

L74 ANSWER 14 OF 39 MEDLINE
ACCESSION NUMBER: 81003447 MEDLINE
DOCUMENT NUMBER: 81003447
TITLE: [Current concept of diagnosis and therapy of acute pancreatitis (author's transl)].
Aktueller Stand von Diagnostik und Therapie der akuten Pankreatitis.
AUTHOR: Lankisch P G; Koop H
SOURCE: DEUTSCHE ZEITSCHRIFT FUR VERDAUUNGS- UND STOFFWECHSELKRANKHEITEN, (1980) 40 (2) 88-100. Ref: 69
Journal code: ED2. ISSN: 0012-1053.
PUB. COUNTRY: GERMANY, EAST: German Democratic Republic
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)

LANGUAGE: German
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198101
AB Acute pancreatitis cannnot be diagnosed only by a single sign, symptom or laboratory determination, but on the basis of several clinical and biochemical findings. X-ray examinations and sonography are of limited diagnostic value in the initial phase. --Prognostic signs are helpful in the early evaluation of the course of the disease. --Intensive care in the initial stage is a decisive principle for adequate therapy. --The effect of hormonal and non-hormonal inhibition of pancreatic secretion or enzyme inhibition has not been proven sufficiently until now or has already been shown to be uneffective in controlled studies. --In contrast, albumin-, fluid- and electrolyte-replacement as well as pain relief and nasogastric suction in case of ileus are safe therapeutical procedures. --Besides shock renal and respiratory insufficiency are the most feared complications in acute pancreatitis and require early peritoneal dialysis and artificial ventilation including positive end expiratory pressure.

L74 ANSWER 15 OF 39 MEDLINE
ACCESSION NUMBER: 80068591 MEDLINE
DOCUMENT NUMBER: 80068591
TITLE: [Uremic pericarditis. Therapy and complications]. Uramische Perikarditis. Therapie und Komplikationen.
AUTHOR: Frei D; Willimann P; Binswanger U
SOURCE: DEUTSCHE MEDIZINISCHE WOCHENSCHRIFT, (1979 Nov 23) 104 (47) 1662-3.
Journal code: ECL. ISSN: 0012-0472.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: German
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198004

L74 ANSWER 16 OF 39 MEDLINE
ACCESSION NUMBER: 80049118 MEDLINE
DOCUMENT NUMBER: 80049118
TITLE: Pericarditis in renal failure.
AUTHOR: Anonymous
SOURCE: HEART AND LUNG, (1979 Nov-Dec) 8 (6) 1139.
Journal code: G2V.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Nursing Journals
ENTRY MONTH: 198003

L74 ANSWER 17 OF 39 MEDLINE
ACCESSION NUMBER: 79155425 MEDLINE
DOCUMENT NUMBER: 79155425
TITLE: [Uremic pericarditis. Preliminary evaluation of treatment with indomethacin (author's transl)].
Pericarditis uremica. Valoracion inicial del tratamiento con indometacina.
AUTHOR: Pascual Turon R; Pascual Figueras J M; Garcia Rafanell J M; Marques Vidal A; Franquesa Salvador J
SOURCE: MEDICINA CLINICA, (1979 Feb 10) 72 (3) 89-92.
Journal code: LTQ. ISSN: 0025-7753.
PUB. COUNTRY: Spain
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Spanish
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197908
AB Numerous therapeutic schemes have been proposed for pericarditis, whether or not accompanied by pericardial effusion in patients with terminal chronic renal insufficiency of subjects on periodic hemodialysis. All of

the authors agree that dialysis must be initiated, or at least must not be interrupted once it is begun. There is some disagreement over the system that should be used (peritoneal dialysis or hemodialysis). Anti-inflammatory drugs have been used in association, since the condition is an inflammatory disease. Five episodes of pericarditis with daily hemodialysis and local heparine were treated, plus five other cases with the addition of 3 mg indomethacin/kg/day for 8 days. No secondary effects of indomethacin were reported. A definite reduction in the duration of pain, fever, pericardial rub, and increase in the size of the cardiac shadow was seen in the episodes treated with the association of indomethacin. This furthermore involved the number of days the patient was subjected to hemodialysis. Partial pericardiectomy was practiced on two patients not treated with indomethacin. The later course of the patients treated with indomethacin was more favorable since pericardial effusion did not lead to significant hemodynamic symptoms. There were no recurrences or other complications.

L74 ANSWER 18 OF 39 MEDLINE
ACCESSION NUMBER: 77259002 MEDLINE
DOCUMENT NUMBER: 77259002
TITLE: [Treatment of hypercalcemia].
Le traitement des hypercalcemies.
AUTHOR: Godeau P; Wechsler B; Lambrozo J
SOURCE: SEMAINE DES HOPITAUX, (1977 Jun 23) 53 (24) 1405-9.
Journal code: ULD. ISSN: 0037-1777.
PUB. COUNTRY: France
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197712
AB Hypercalcemia may have various causes. I should nevertheless be rapidly treated. Among recent treatmens, we may quote diuresis with furosemide, calcitonin, mithramycin, which are the most effective. More recently indomethacin has been used and may be more specific for neoplastic hypercalcemia. These various treatments should be proposed depending on the level of serum calcium, the rapidity of onset and the presumed cause.

L74 ANSWER 19 OF 39 MEDLINE
ACCESSION NUMBER: 69284184 MEDLINE
DOCUMENT NUMBER: 69284184
TITLE: [Therapeutic possibilities in chronic glomerulonephritis].
Behandlungsmoglichkeiten bei der chronischen Glomerulonephritis.
AUTHOR: Brass H
SOURCE: MUNCHENER MEDIZINISCHE WOCHENSCHRIFT, (1969 Aug 29) 111 (35) 1759-66.
Journal code: MMW. ISSN: 0027-2973.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: German
FILE SEGMENT: Priority Journals
ENTRY MONTH: 196912

L74 ANSWER 20 OF 39 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 2
ACCESSION NUMBER: 1999:464780 BIOSIS
DOCUMENT NUMBER: PREV199900464780
TITLE: D-glucose increases the synthesis of tissue-type plasminogen activator (t-PA) in human **peritoneal** mesothelial cells.
AUTHOR(S): Sitter, Thomas (1); Mandl-Weber, Sonja; Woernle, Markus; Haslinger, Bettina; Goedde, Martin; Kooistra, Teake
CORPORATE SOURCE: (1) Medizinische Klinik, Klinikum Innenstadt, Universitaet Muenchen, Ziemssenstrasse 1, D-80336, Muenchen Germany
SOURCE: Thrombosis and Haemostasis, (Sept., 1999) Vol. 82, No. 3, pp. 1171-1176.

ISSN: 0340-6245.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Physical and chemical irritation of the **peritoneum** through glucose-based hyperosmolar **dialysis** solutions results in a nonbacterial serositis with fibrinous exudation. Thereby, human **peritoneal** mesothelial cells (HMC) play an important role in maintaining the balance between the **peritoneal** generation and degradation of fibrin by expressing the fibrinolytic enzyme tissue-type plasminogen activator (t-PA) as well as the specific plasminogen activator inhibitor-1 (PAI-1). In this study, we analyzed the effect of D-glucose and metabolically inert monosaccharides on the synthesis of t-PA and PAI-1 in cultured HMC. Incubation of HMC with D-glucose or the metabolically inert monosaccharides mannitol and L-glucose (5-90 mM) resulted in a time- and concentration-dependent increase in t-PA mRNA expression and antigen secretion without affecting PAI-1 synthesis. A similar effect was evident when HMC were first exposed sequentially to pooled spent **peritoneal dialysis** effluent for up to 4 hours, andsubsequently incubated for 20 hours in control medium. The stimulating effect of high D-glucose on t-PA expression in HMC was prevented by treating the cells with different **protein kinase C (PKC) inhibitors** (Ro 31-8220, Go 6976), but could not be mimicked by the PKC-activating phorbol ester PMA, indicating that this effect of high glucose is dependent on PKC activity, but not mediated through **PKC** activation. Also, using specific **inhibitors** (PD 98059, SB 203580) and activators (PMA, anisomycin, IL-1alpha) of the major routes of the mitogen-activated protein kinases (MAPKs) cascade, we found no evidence for a role of this cascade in regulating t-PA expression in HMC. We conclude that hyperosmolarity induces t-PA (but not PAI-1) in HMC via a regulatory mechanism that requires active PKC, but that does not involve a major pathway in the MAPK cascade.

L74 ANSWER 21 OF 39 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 3
ACCESSION NUMBER: 1998:519057 BIOSIS
DOCUMENT NUMBER: PREV199800519057
TITLE: High glucose increases prostaglandin E2 synthesis in human **peritoneal** mesothelial cells: Role of hyperosmolarity.
AUTHOR(S): Sitter, Thomas (1); Haslinger, Bettina; Mandl, Sonja; Fricke, Harald; Held, Eckhard; Sellmayer, Alois
CORPORATE SOURCE: (1) Med. Klinik, Klinikum Innenstadt Univ. Muenchen, Ziemssenstrasse 1, D-80336 Munich Germany
SOURCE: Journal of the American Society of Nephrology, (Nov., 1998) Vol. 9, No. 11, pp. 2005-2012.
ISSN: 1046-6673.
DOCUMENT TYPE: Article
LANGUAGE: English
AB **Peritoneal** mesothelial cells are considered the predominant source of **peritoneal** prostanoid formation because they represent the largest resident cell population in the **peritoneal** cavity. The present study was designed to evaluate the effect of D-glucose, which is widely used in commercially available **peritoneal dialysis** fluids as an osmotic compound, on the synthesis of prostaglandins in cultured human mesothelial cells (HMC). Analysis of eicosanoid synthesis in HMC by reversed-phase HPLC revealed that 6-keto-PGF1alpha, the spontaneous hydrolysis product of prostacyclin (PGI2), and prostaglandin E2 (PGE2) were the main eicosanoids produced. Addition of D-glucose resulted in a time- and concentration-dependent (30 to 120 mM) increase in PGE2 production in HMC (24 h, 90 mM: 3.9 +- 0.5 ng/105 cells versus 2.3 +- 0.3 in untreated cells; $P < 0.05$). Mannitol (90 mM) or L-glucose (90 mM), nonmetabolizable osmotic compounds, also led to a significant ($P < 0.05$) but less intense increase in PGE2 synthesis (3.3 +- 0.4 and 3.2 +- 0.5 ng/105 cells, respectively). Increased PGE2

synthesis was completely blunted by coincubation with the specific **protein kinase C (PKC) inhibitor** Ro 31-8220 or downregulation of PKC activity by preincubation with phorbol myristate acetate for 16 h. Furthermore, coincubation with PD 98059, an inhibitor of the mitogen-activated protein kinase/extracellular signal-regulated kinase pathway, also inhibited increased PGE2 synthesis by D-glucose or mannitol. In contrast, the iso-osmolar glucose polymer icodextrin, which is used as an alternative to D-glucose in **peritoneal dialysis** solutions, had no effect on PGE2 synthesis. These data indicate that D-glucose and metabolically inert sugars increase PGE2 synthesis in HMC at least in part by hyperosmolarity and that this effect requires activation of PKC and the mitogen-activated protein kinase/extracellular signal-regulated kinase pathway of intracellular signaling.

L74 ANSWER 22 OF 39 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 2000:151816 BIOSIS
DOCUMENT NUMBER: PREV200000151816
TITLE: Protein kinase C enhances the rapidly activating delayed rectifier potassium current, IKr, through a reduction in C-type inactivation in guinea-pig ventricular myocytes.
AUTHOR(S): Heath, B. M. (1); Terrar, D. A.
CORPORATE SOURCE: (1) University Department of Pharmacology, Mansfield Road, Oxford, OX1 3QT UK
SOURCE: Journal of Physiology (Cambridge)., (Feb. 1, 2000) Vol. 522, No. 3, pp. 391-402.
ISSN: 0022-3751.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB 1. The rapidly activating delayed rectifier potassium current, IKr, was studied in guinea-pig ventricular myocytes in the presence of thiopentone, which blocks the more slowly activating component of the delayed rectifier potassium current, IKs, and using whole cell perforated patch clamp or switched voltage clamp with sharp electrodes to minimise intracellular **dialysis**. 2. Activation of protein kinase A (PKA) by isoprenaline or forskolin caused an increase in IKr tail currents. Following a 300 ms depolarising step to +20 mV, mean tail current amplitude was increased 47 +- 12% by isoprenaline, and 73 +- 13% by forskolin. No increase in IKr was observed when IKr was studied using whole cell ruptured patch clamp and there was no change in the reversal potential of IKr in the presence of isoprenaline. 3. The rectification of the current sensitive to E4031, a selective IKr blocker, was markedly reduced in the presence of isoprenaline and the region of negative slope was absent. This is consistent with a reduction in the inactivation of IKr and was supported by the finding that IKr, in the presence of isoprenaline, was somewhat less sensitive to block. E4031 (5 muM) blocked only 81 +- 5% of IKr in the presence of isoprenaline compared to 100 +- 0% in control. 4. The forskolin- and isoprenaline-induced increases in IKr were inhibited by staurosporine and by the selective protein kinase C (PKC) inhibitor **bisindolylmaleimide** I. Direct activation of PKC by phorbol dibutyrate increased IKr tail currents by 24 +- 5%. Both the isoprenaline-and forskolin-induced increases in IKr were inhibited when calcium entry was reduced by block of ICa with nifedipine or when myocytes were pre-incubated in BAPTA-AM. 5. The selective PKA inhibitor KT5720 prevented the isoprenaline-induced increase in IKr only when the increase in ICa was also suppressed. 6. These data show a novel mechanism of regulation of IKr by PKC and this kinase was activated by beta-adrenoceptor stimulation. IKr seems to be enhanced through a reduction in the C-type inactivation which underlies the rectification of the channel and such a mechanism may occur in other channels with this type of inactivation.

L74 ANSWER 23 OF 39 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 2000:524483 BIOSIS
DOCUMENT NUMBER: PREV200000524483

TITLE: D-glucose increases the synthesis of tissue-type plasminogen activator (t-PA) in human **peritoneal** mesothelial cells.
AUTHOR(S): Sitter, T. (1); Mandl-Weber, S.; Woernle, M.; Haslinger, B.; Goedde, M.; Kooistra, T.
CORPORATE SOURCE: (1) Klinikum Innenstadt, Ludwig-Maximilians-Universitaet, Munich Germany
SOURCE: Kidney & Blood Pressure Research, (1999) Vol. 22, No. 4-6, pp. 328-329. print.
Meeting Info.: Joint Scientific Meeting of the Society for Nephrology and the German Working Group for Clinical Nephrology Freiburg, Germany September 18-21, 1999
ISSN: 1420-4096.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L74 ANSWER 24 OF 39 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1999:311749 BIOSIS
DOCUMENT NUMBER: PREV199900311749
TITLE: Regulation ~~of L-type Ca2+ channels~~ in rabbit portal vein by G protein alphas and betagamma subunits.
AUTHOR(S): Zhong, Juming; Dessauer, Carmen W.; ~~Keef~~, Kathleen D.; Hume, Joseph R. (1)
CORPORATE SOURCE: (1) Department of Physiology and Cell Biology/351, University of Nevada School of Medicine, Reno, NV, 89557 USA
SOURCE: Journal of Physiology (Cambridge), ~~(May 15, 1999)~~ Vol. 517, No. 1, pp. 109-120.
ISSN: 0022-3751.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB 1. The effect of purified G protein subunits alphas and betagamma on L-type Ca2+ channels in vascular smooth muscle and the possible pathways involved were investigated using freshly isolated smooth muscle cells from rabbit portal vein and the whole-cell patch clamp technique. 2. Cells **dialysed** with either Galphas or Gbetagamma exhibited significant increases in peak Ba2+ current (IBa) density (148% and 131%, respectively) compared with control cells. The combination of Galphas and Gbetagammafurther increased peak IBa density (181%). Inactive Galphas and Gbetagamma did not have any effect on Ca2+ channels. 3. The stimulatory effect of Galphas on peak IBa was entirely abolished by the protein kinase A inhibitor Rp-8-Br-cAMPS, or the adenylyl cyclase inhibitor SQ 22536. On the other hand, the stimulatory response of Ca2+ channels to Gbetagamma was not affected by the protein kinase A inhibitors Rp-8-Br-cAMPS and KT 5720, or by the Ca2+-dependent protein kinase C inhibitor ~~bisindolylmaleimide~~ 1, but was completely blocked by the protein kinase C inhibitor calphostin C. Pretreatment of cells with phorbol 12-myristate 13-acetate for over 18 h prevented the stimulatory effect of Gbetagamma on peak IBa. In addition, acute application of phorbol 12,13-dibutyrate enhanced peak IBa density in control cells, which could be entirely blocked by calphostin C. 4. These data indicate that enhancement of Ba2+ currents by Galphas and Gbetagamma can be attributed to increased activity of protein kinase A and protein kinase C, respectively. No direct membrane-delimited pathway for Ca2+ channel regulation by activated Gs proteins could be detected in vascular smooth muscle cells.

L74 ANSWER 25 OF 39 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1998:387791 BIOSIS
DOCUMENT NUMBER: PREV199800387791
TITLE: PKC regulation of cardiac CFTR Cl- channel function in ~~guinea~~ pig ventricular myocytes.
AUTHOR(S): Middleton, Lisa M.; Harvey, Robert D. (1)
CORPORATE SOURCE: (1) Dep. Physiol. Biophys., Case Western Res. Univ., 2109

Adelbert Road, Cleveland, OH 44106-4970 USA
SOURCE: American Journal of Physiology, (July, 1998) Vol. 275, No. 1 PART1, pp. C293-C302.
ISSN: 0002-9513.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The role of protein kinase C (PKC) in regulating the protein kinase A (PKA)-activated Cl- current conducted by the cardiac isoform of the cystic fibrosis transmembrane conductance regulator (cCFTR) was studied in guinea pig ventricular myocytes using the whole cell patch-clamp technique. Although stimulation of endogenous PKC with phorbol 12,13-dibutyrate (PDBu) alone did not activate this Cl- current, even when intracellular **dialysis** was limited with the perforated patch-clamp technique, activation of PKC did elicit a significant response in the presence of PKA-dependent activation of the current by the beta-adrenergic receptor agonist isoproterenol. PDBu increased the magnitude of the Cl- conductance activated by a supramaximally stimulating concentration of isoproterenol by 21 +- 3.3% (n = 9) when added after isoproterenol and by 36 +- 16% (n = 14) when introduced before isoproterenol. 4alpha-Phorbol 12,13-didecanoate, a phorbol ester that does not activate PKC, did not mimic these effects. Preexposure to chelerythrine or **bisindolylmaleimide**, two highly selective inhibitors of PKC, significantly reduced the magnitude of the isoproterenol-activated Cl- current by 79 +- 7.7% (n = 11) and 52 +- 10% (n = 8), respectively. Our results suggest that although acute activation of endogenous PKC alone does not significantly regulate cCFTR Cl- channel activity in native myocytes, it does potentiate PKA-dependent responses, perhaps most dramatically demonstrated by basal PKC activity, which may play a pivotal role in modulating the function of these channels.

L74 ANSWER 26 OF 39 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1996:151353 BIOSIS
DOCUMENT NUMBER: PREV199698723488
TITLE: Protein kinase C activates ATP-sensitive K+ current in human and rabbit ventricular myocytes.
AUTHOR(S): Hu, Keli; Duan, Dayue; Li, Gui-Rong; Nattel, Stanley (1)
CORPORATE SOURCE: (1) Montreal Heart Inst., 5000 Belanger St. E, Montreal, PQ H1T 1C8 Canada
SOURCE: Circulation Research, (1996) Vol. 78, No. 3, pp. 492-498.
ISSN: 0009-7330.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Mediators involved in ischemic preconditioning, such as adenosine and norepinephrine, can activate protein kinase C (PKC), and a variety of observations suggest that both PKC and ATP-sensitive K+ current (I-KATP) play essential roles in ischemic preconditioning. PKC is therefore a candidate to link receptor binding to I-KATP activation, but it has not been shown whether and how PKC can activate I-KATP in the heart. The present study was designed to determine whether PKC can activate I-KATP in rabbit and human ventricular myocytes. Under conditions designed to minimize Na+ and Ca-2+ currents, **dialysis** of rabbit ventricular myocytes with pipette solutions containing reduced (ATP) elicited I-KATP, with a 50% effective concentration (EC-50) of 260 mu-mol/L. In cells that failed to show I-KATP under control conditions, superfusion with 1 mu-mol/L phorbol 12,13-didecanoate (PDD) elicited I-KATP in a fashion that depended on pipette (ATP), with an (ATP) EC-50 of 601 mu-mol/L. PDD-induced I-KATP activation was concentration dependent, with an EC-50 of 7.1 nmol/L. The highly selective PKC inhibitor **bisindolylmaleimide** totally prevented I-KATP activation by PDD, and in blinded experiments, 1 mu-mol/L PDD elicited I-KATP in eight of nine cells, whereas its non-PKC-stimulating analogue 4-alpha-PDD failed to elicit I-KATP in any of the five cells tested (P=.003). Similar experiments were conducted in human ventricular myocytes and showed that 0.1 mu-mol/L PDD elicited I-KATP at pipette (ATP) of 100 and 400 mu-mol/L (five of five cells at each concentration) but not at 1 mmol/L (ATP) (none of five cells). We conclude that PKC activates I-KATP in rabbit and human

ventricular myocytes by reducing channel sensitivity to intracellular ATP. This finding has potentially important implications for understanding the mechanisms of ischemic preconditioning.

L74 ANSWER 27 OF 39 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1995:450633 BIOSIS
DOCUMENT NUMBER: PREV199598464933
TITLE: Depletion-activated calcium current is inhibited by protein kinase in RBL-2H3 cells.
AUTHOR(S): Parekh, Anant B.; Penner, Reinhold
CORPORATE SOURCE: Dep. Membrane Biophysics, Max Planck Inst. Biophsyical Chem., Am Fassberg, D-37707 Goettingen Germany
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1995) Vol. 92, No. 17, pp. 7907-7911.
ISSN: 0027-8424.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Whole-cell patch-clamp recordings and single-cell Ca-2+ measurements were used to study the control of Ca-2+ entry through the Ca-2+ release-activated Ca-2+ influx pathway (I-CRAC) in rat basophilic leukemia cells. When intracellular inositol 1,4,5-trisphosphate (InsP-3)-sensitive stores were depleted by **dialyzing** cells with high concentrations of InsP-3, I-CRAC inactivated only slightly in the absence of ATP. Inclusion of ATP accelerated inactivation 2-fold. The inactivation was increased further by the ATP analogue adenosine 5'-(gamma-thio)triphosphate, which is readily used by protein kinases, but not by 5'-adenylyl imidodiphosphate, another ATP analogue that is not used by kinases. Neither cyclic nucleotides nor inhibition of calmodulin or tyrosine kinase prevented the inactivation. Staurosporine and **bisindolylmaleimide**, protein kinase C inhibitors, reduced inactivation of I-CRAC, whereas phorbol ester accelerated inactivation of the current. These results demonstrate that a protein kinase-mediated phosphorylation, probably through protein kinase C, inactivates I-CRAC. Activation of the adenosine receptor (A-3 type) in RBL cells did not evoke much Ca-2+ influx or systematic activation of I-CRAC. After protein kinase C was blocked, however, large I-CRAC was observed in all cells and this was accompanied by large Ca-2+ influx. The ability of a receptor to evoke Ca-2+ entry is determined, at least in part, by protein kinase C. Antigen stimulation, which triggers secretion through a process that requires Ca-2+ influx, activated I-CRAC. The regulation of I-CRAC by protein kinase will therefore have important consequences on cell functioning.

L74 ANSWER 28 OF 39 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1995:112746 BIOSIS
DOCUMENT NUMBER: PREV199598127046
TITLE: Cortisol Inhibition of Calcium Currents in Guinea Pig Hippocampal CA1 Neurons via G-Protein-coupled Activation of Protein Kinase C.
AUTHOR(S): Ffrench-Mullen, Jariath M. H.
CORPORATE SOURCE: Dep. Pharmacol., Zeneca Pharmaceuticals Group, Zeneca Inc., Wilmington, DE 19897 USA
SOURCE: Journal of Neuroscience, (1995) Vol. 15, No. 1 PART 2, pp. 903-911.
ISSN: 0270-6474.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The inhibition of voltage-activated Ca-2+ channel currents by cortisol (hydrocortisone), the principal glucocorticoid in man and guinea pig, was examined in freshly dissociated pyramidal neurons from the adult guinea pig hippocampal CA1 region using whole-cell voltage-clamp recordings. Steady-state inhibition by cortisol of the peak Ca-2+ channel current evoked by depolarization from -80 to -10 mV increased in a concentration-dependent fashion, with a maximal inhibition of 63 +- 4% of the total current at 100 mu-M. Cortisone had a maximal 17 +- 2% inhibition at 10 mu-M. Corticosterone and the metabolite

allotetrahydrodeoxycorticosterone exhibited a plateau of inhibition of around 15% and 25%, respectively, between 10 pM and 100 nM; both compounds continued to inhibit at concentrations gt 10-7 M. Analysis of tail currents at -80 mV showed that cortisol and corticosterone had no effect on the voltage-dependent activation or deactivation of the Ca-2+ channel current. However, cortisol slowed the activation of the current. Cortisol inhibited both the N-type or omega-conotoxin (CgTX)-sensitive,and the L-type or nifedipine (NIF)-sensitive Ca-2+ channel current but had no effect on the CgTX/NIF-insensitive Ca-2+ channel current. In neurons isolated from pertussis toxin (PTX)-treated animals, the cortisol inhibition was significantly diminished. Intracellular dialysis with GDP-beta-S (500 mu-M) or with the specific inhibitors of protein kinase C (PKC), the pseudosubstrate PKC inhibitor (PKCI 19-31) (2 mu-M) and **bisindolylmaleimide** (BIS) (1 mu-M) significantly diminished the cortisol inhibition of the Ca-2+ channel current. The specific inhibitor of cAMP-dependent protein kinase (PKA) inhibitor, Rp-cAMPS (100 mu-M) had no effect. These results demonstrate that cortisol is a potent modulator of both the CgTX- and NIF-sensitive Ca-2+ channel current but not the CgTX/NIF-insensitive current. This inhibition is via a PTX-sensitive G-protein-coupled mechanism associated with the activation of PKC.

L74 ANSWER 29 OF 39 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1994:229207 BIOSIS
DOCUMENT NUMBER: PREV199497242207
TITLE: Neurosteroids modulate calcium currents in hippocampal CA1 neurons via a pertussis toxin-sensitive G-protein-coupled mechanism.
AUTHOR(S): Ffrench-Mullen, Jarlath M. H. (1); Danks, Petra; Spence, Katherine T.
CORPORATE SOURCE: (1) Dep. Pharmacol., Zeneca Pharmaceuticals Group, Zeneca Inc., Wilmington, DE 19897 USA
SOURCE: Journal of Neuroscience, (1994) Vol. 14, No. 4, pp. 1963-1977.
ISSN: 0270-6474.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The inhibition of Ca-2+ channel currents by endogenous brain steroids was examined in freshly dissociated pyramidal neurons from the adult guinea pig hippocampal CA1 region. The steady-state inhibition of the peak Ca-2+ channel current evoked by depolarizing steps from -80 to -10 mV occurred in a concentration-dependent manner with the following IC-50 values: pregnenolone sulfate (PES), 11 nM; pregnenolone (PE), 130 nM; and allotetrahydrocorticosterone (THCC), 298 nM. THCC, PE, and PES depressed a fraction of the Ca-2+ channel current with a maximal inhibition of 60% of the total current. However, substitution of an acetate group for the concomitant extracellular perfusion of PES showed normal inhibitory activity, suggesting that the steroid binding site can only be accessed extracellularly. Analysis of tail currents at -80 mV demonstrated that THCC and PES slowed the rate of Ca-2+ current activation and deactivation with no change in the voltage dependence of activation. Inhibition of the Ca-2+ channel current by THCC and PES was voltage dependent. THCC primarily inhibits the omega-conotoxin (CgTX)sensitive or N-type Ca-2+ channel current. PE was nonselective in inhibiting both the CgTX- and the nifedipine (NIF)sensitive Ca-2+ channel current. These neurosteroids had no effect on the CgTX/NIF-insensitive current. In neurons isolated from pertussis toxin (PTX)-treated animals by chronic intracerebroventricular infusion (1000 ng/ 24 hr for 48 hr), the Ca-2+ channel current inhibition by PES, PE, and THCC was significantly diminished. Intracellular **dialysis** with GDP-beta-S (500 mu-M) also significantly diminished the neurosteroid inhibition of the Ca-2+ channel current. Intracellular **dialysis** with the general kinase inhibitors H-7 (100 mu-M), staurosporine (400 nM), and a 20 amino acid protein kinase inhibitor (1 mu-M) also significantly prevented the THCC and PES inhibition of the Ca-2+ channel current. Intracellular **dialysis** with the more specific inhibitors of protein kinase C (PKC), the pseudosubstrate

inhibitor (PKCI 19-36) (1-2 mu-M) and **bisindolylmaleimide** (1 mu-M) significantly diminished the THCC and PE inhibition of the Ca-2+ channel current. Rp-cAMPS (100 mu-M), a specific inhibitor of cAMP-dependent protein kinase (PKA), had no effect on the THCC and PE inhibition of the Ca-2+ current. These results demonstrate that neurosteroids, acting at a membrane receptor site, are potent modulators of either the CgTX- and/or the NIF-sensitive Ca-2+ channel current but not the CgTX/NIF-insensitive current. Furthermore, the Ca-2+ channel current inhibition is via a PTX-sensitive G-protein-coupled mechanism associated with the activation of PKC. Thus, inhibition of Ca-2+ channel currents by neurosteroids may participate in the regulation of synaptic processes such as modulation of neuronal activity and/or neurotransmitter release-associated mechanisms via a G-protein mechanism(s).

L74 ANSWER 30 OF 39 CAPLUS COPYRIGHT 2000 ACS DUPLICATE 1
ACCESSION NUMBER: 2000:645802 CAPLUS
DOCUMENT NUMBER: 133:217700
TITLE: **Inhibition** of **protein kinase C** to treat permeability failure in **peritoneal dialysis** for kidney failure
INVENTOR(S): King, George Liang
PATENT ASSIGNEE(S): Joslin Diabetes Center, Inc., USA
SOURCE: PCT Int. Appl., 18 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000053013	A1	20000914	WO 2000-US6405	20000310

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-124043 19990312
AB The invention features a method of treating a subject having a permeability disjunction whereby an **inhibitor** of PKC (**protein kinase C**), e.g. PKC .beta., is added to the **peritoneal dialysis** fluid and administered to a subject having renal failure. The invention also features an improved **peritoneal dialysis** fluid and methods of making such **dialysis** fluid.
REFERENCE COUNT: 2
REFERENCE(S): (1) Elliott; US 5736564 A 1998 CAPLUS
(2) Elliott; US 5929106 A 1999 CAPLUS

L74 ANSWER 31 OF 39 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:126014 CAPLUS
DOCUMENT NUMBER: 126:223790
TITLE: Intraperitoneal coagulation and fibrinolysis during inflammation: in vivo and in vitro observations
AUTHOR(S): Sitter, T.; Goedde, M.; Spannagl, M.; Fricke, H.; Kooistra, T.
CORPORATE SOURCE: Medizinische Klinik, Klinikum Innenstadt, University of Munich, Munchen, D-80336, Germany
SOURCE: Fibrinolysis (1996), 10(Suppl. 2), 99-109

CODEN: FBRIE7; ISSN: 0268-9499
PUBLISHER: Churchill Livingstone
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors used continuous **peritoneal dialysis** (CAPD) as a model to study i.p. fibrin turnover during peritonitis. Activation markers of coagulation and fibrinolysis including prothrombin fragment F1+2, thrombin-antithrombin III complex (TAT), fibrin monomer (FM), and fibrin degrdn. products (FbDP) were measured in the **peritoneal dialysis** effluents from 23 CAPD patients. In the **dialyzate** of patients who had not suffered from peritonitis during the last 6 mo the authors found remarkably high levels of F1+2, TAT and FM concomitant with a high concn. of FbDP, indicating a high rate of i.p. fibrin turnover. The balance between **peritoneal** generation and degrdn. of fibrin was disturbed in untreated patients with acute peritonitis, who had significantly higher levels of coagulation markers and a higher ratio between FM and FbDP. To evaluate the role of mesothelial cells (MC) in the high **peritoneal** fibrin turnover, the authors investigated the expression of tissue-type plasminogen activator (t-PA), urokinase-type plasminogen activator (u-PA), plasminogen activator **inhibitor** type-1 (PAI-1) and tissue factor (TF) in cultured human **peritoneal** MC under basal conditions and after exposure to tumor necrosis factor .alpha. (TNF.alpha.), interleukin-1.alpha. (IL-1.alpha.) or bacterial lipopolysaccharide (LPS). The exposure of MC to TNF.alpha., or to a lesser extent, IL-1.alpha. or LPS, reduced their fibrinolytic activity by decreasing t-PA prodn. and increasing PAI-1 synthesis. Furthermore the addn. of TNF.alpha. resulted in an activation of the coagulation cascade by the expression of TF. The authors found that the isoflavone compd. genistein (25.mu.g/mL) prevented the TNF.alpha.-induced expression of PAI-1 and TF, while also slightly counteracting the decrease in t-PA synthesis. The **protein kinase C inhibitor**, Ro 31-8220 (3.mu.M), only moderately opposed the TNF.alpha.-induced changes in t-PA and PAI-1 synthesis, but completely prevented the induction of TF mRNA. In summary the authors' in vitro findings explain the disbalance between i.p. coagulation and fibrinolysis during peritonitis in vivo. To restore the balance between fibrinolysis and coagulation under inflammatory conditions attempts to interfere with the TNF.alpha. signaling pathway could be a new therapeutic approach.

L74 ANSWER 32 OF 39 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:661092 CAPLUS
DOCUMENT NUMBER: 123:47892
TITLE: Method for inactivating pathogens using reaction products of immobilized peroxidase
INVENTOR(S): Kessler, Jack
PATENT ASSIGNEE(S): Symbollon Corporation, USA
SOURCE: U.S., 7 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5419902	A	19950530	US 1993-92605	19930716
EP 745327	A1	19961204	EP 1995-108235	19950529
R: DE, ES, FR, GB, IT, SE				
JP 08322915	A2	19961210	JP 1995-130861	19950529

PRIORITY APPLN. INFO.: US 1993-92605 19930716

AB This invention relates to a method for inactivating pathogens using the peroxidase enzyme. The peroxidase enzyme is reacted with hydrogen peroxide or a source of hydrogen peroxide and an iodide anion to generate reaction products which are sepd. from the peroxidase enzyme and then used to inactivate pathogenic organisms. The peroxidase is immobilized on a

solid support, e.g. activated latex particles. Inactivation of e.g. Staphylococcus aureus treated with immobilized peroxidase reaction products is described.

L74 ANSWER 33 OF 39 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1993:77393 CAPLUS
DOCUMENT NUMBER: 118:77393
TITLE: Effects of some metal-ATP complexes on sodium-calcium exchange in internally **dialyzed** squid axons
AUTHOR(S): DiPolo, Reinaldo; Beauge, Luis
CORPORATE SOURCE: Cent. Biofis. Bioquim., IVIC, Caracus, 1020A, Venez.
SOURCE: J. Physiol. (London) (1993), 462, 71-86
CODEN: JPHYA7; ISSN: 0022-3751
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Extracellular Na+ (Na0+)-dependent Ca2+ efflux (forward Na+-Ca2+ exchange), and in some cases the intracellular Na+ (Nai+)-dependent Ca2+ influx (reverse Na+-Ca2+ exchange) were measured in internally dialyzed squid axons under membrane potential control. The authors tested the effect on the Na+-Ca2+ exchange of the MgATP analog bidentate chromium ATP (CrATP), substrate of several kinases, and cobalt tetrammine ATP (Co(NH3)4ATP), a poor substrate of most kinases. CrATP completely blocked the MgATP and MgATP-.gamma.-S (ATP-.gamma.-S) stimulation of the Na0+-dependent Ca2+ efflux (forward exchange) and the Nai+-dependent Ca2+ influx (reverse exchange). The analog only blocked the nucleotide-dependent fraction of the Na+-Ca2+ exchange without modifying any kinetic parameters of the exchange reactions. The effects of CrATP were fully reversible with a very slow time const. (t1/2 .apprx.30 min). The MgATP stimulation of the Na+-Ca2+ exchange was completely satd. at 1 mM. Higher MgATP concns. (<15 mM) had no addnl. effects. Pentalysine (internal or external), the **protein kinase C inhibitor** H-7 and several calmodulin **inhibitors** did not **inhibit** Na+-Ca2+ either in the absence or presence of MgATP. The results do not agree with the idea of an aminophospholipid translocase being responsible for the ATP stimulation of the Na+-Ca2+ exchange in squid axons; they suggest that this is due to the action of a kinase system.

L74 ANSWER 34 OF 39 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998242033 EMBASE
TITLE: Activation of a nonspecific cation current in rat cultured retinal pigment epithelial cells: Involvement of a G(.alpha.i) subunit protein and the mitogen-activated protein kinase signalling pathway.
AUTHOR: Ryan J.S.; Kelly M.E.M.
CORPORATE SOURCE: M.E.M. Kelly, Department Pharmacology, Dalhousie University, Halifax, NS B3H 4H7, Canada
SOURCE: British Journal of Pharmacology, (1998) 124/6 (1115-1122).
Refs: 45
ISSN: 0007-1188 CODEN: BJPCBM
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 012 Ophthalmology
029 Clinical Biochemistry
030 Pharmacology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB 1. Whole-cell patch-clamp recording techniques were used to investigate the G protein subtype and related signalling molecules involved in activation of a nonspecific cation (NSC) current in rat cultured retinal pigment epithelial (RPE) cells. 2. Under control conditions, in 130 mM NaCl with K+ aspartate in the pipette, cytosolic dialysis with guanosine-5'-O-(3-triphosphate) (GTP.gamma.S, 0.1 mM) activated a large non-inactivating NSC current in 80% of the cells recorded from. 3. Loading RPE cells with antibodies (10 .mu.g-ml-1) against the .alpha. subunit of all PTX-sensitive G proteins (G(.alpha.i/o/t/z)) reduced NSC current

activation to 11%, while loading RPE cells with antibodies directed specifically against the .alpha. subunits of the G(i) subclass (G(.alpha.i-3)) completely abolished current activation. In RPE cells loaded with anti-G(.alpha.s) activation of the NSC current was unaffected. 4. Investigation of the potential downstream mediators in the G(.alpha.i) NSC channel pathway revealed that activation of the cation conductance was unaffected by treatment of RPE cells with the selective protein kinase C inhibitor GF 109203X (3 .mu.M) or the selective CaM kinase II inhibitor KN-93 (50 .mu.M). However, NSC current activation was delayed and the current amplitude reduced in the presence of the nonselective kinase inhibitor H-7 (100 .mu.M) or the selective inhibitor of MAPKK (MEK) activation, PD 98059 (50 .mu.M). 5. In the absence of GTP.gamma.S, the NSC current was not activated by superfusion of the cells with the cyclic GMP kinase activator dibutyryl-cyclic GMP or with the adenylate cyclase activator forskolin. 6. These results support the involvement of a G protein of the G(.alpha.i) subclass in the activation of a NSC current in rat RPE cells, and suggest a potential modulatory role for MAP kinase-dependent phosphorylation in current regulation.

L74 ANSWER 35 OF 39 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 97147280 EMBASE
DOCUMENT NUMBER: 1997147280
TITLE: Ionic mechanism of the effects of hydrogen peroxide in rat ventricular myocytes.
AUTHOR: Ward C.A.; Giles W.R.
CORPORATE SOURCE: W.R. Giles, Department Physiology and Biophysics, University of Calgary, Faculty of Medicine, Calgary T2N 4N1, Canada
SOURCE: Journal of Physiology, (1997) 500/3 (631-642).
Refs: 40
ISSN: 0022-3751 CODEN: JPHYA7
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
018 Cardiovascular Diseases and Cardiovascular Surgery
LANGUAGE: English
SUMMARY LANGUAGE: English

AB 1. Whole-cell and amphotericin-perforated patch-clamp techniques have been used to study the effects of hydrogen peroxide (H2O2) on action potentials and underlying ionic currents in single myocytes from the ventricles of adult rat hearts. 2. The results obtained differed markedly depending on the recording method utilized. Conventional whole-cell recordings, in which the myoplasm is dialysed with the contents of the pipette, failed to show any significant effects of H2O2 on the action potential or cell shortening. In contrast, when action potentials were recorded with the amphotericin-perforated patch method, H2O2 (50-200 .mu.M) produced a marked prolongation of the action potential and an increase in cell shortening. 3. Voltage-clamp recordings with the amphotericin-perforated patch method showed that H2O2 caused no significant changes in either the Ca2+-independent transient outward K+ current (I(to)) or the inwardly rectifying K+ current (I(K1)). 4. Application of tetrodotoxin (TTX; 8 x 10-6 M), a Na+ channel blocker, largely inhibited the effects of H2O2 on the action potential. Moreover, anthopleurin A (4 x 10-7 M), which augments Na+ current (I(Na)) by slowing its inactivation, mimicked the effects of H2O2 on the action potential of ventricular myocytes. These effects on I(Na) were also blocked almost completely by TTX. 5. The hypothesis that H2O2 can augment I(Na) by slowing its kinetics of inactivation was tested directly using ensemble recordings from cell-attached macropatches. These results demonstrated a significant enhancement of late opening events when H2O2 (200 .mu.M) was included in the recording pipette. A corresponding slowing of inactivation of the ensemble I(Na) was observed. 6. The possibility that protein kinase C (PKC) is an intracellular second messenger for the observed effects of H2O2 was examined using the blocker bisindolylmaelimide (BIS; 10-7 M). Bath application of BIS prior to H2O2 exposure significantly delayed and also attenuated the development of the action potential prolongation. 7.

These results demonstrate marked electrophysiological effects of H2O2 in rat ventricle. The dependence of these effects on recording methods suggests involvement of an intracellular second messenger, and the results with the PKC inhibitor, BIS, support this possibility. The most prominent effect of H2O2 on the ionic currents which underlie the action potential is a slowing of inactivation of the TTX-sensitive I(Na). Recent molecular studies have demonstrated a PKC phosphorylation site on the rat cardiac Na+ channel isoform and have also shown that PKC activation can slow inactivation of I(Na).

L74 ANSWER 36 OF 39 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95177392 EMBASE
DOCUMENT NUMBER: 1995177392
TITLE: Phosphorylation- and voltage-dependent inhibition of neuronal calcium currents by activation of human D(2(short)) dopamine receptors.
AUTHOR: Brown N.A.; Seabrook G.R.
CORPORATE SOURCE: Department of Pharmacology, Merck Sharp Dohme Research Labs., Neuroscience Research Centre, Eastwick Road,Harlow CM20 2QR, United Kingdom
SOURCE: British Journal of Pharmacology, (1995) 115/3 (459-466). ISSN: 0007-1188 CODEN: BJPCBM
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
008 Neurology and Neurosurgery
030 Pharmacology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB 1. Activation of human D(2(s)) dopamine receptors with quinpirole (10 nM) inhibits .omega.-conotoxin GVIa-sensitive, high-threshold calcium currents when expressed in differentiated NG108-15 cells (55% inhibition at +10 mV). This inhibition was made irreversible following intracellular dialysis with the non-hydrolysable guanosine triphosphate analogue GTP-.gamma.-S (100 .mu.M), and was prevented by pretreatment with pertussis toxin (1 .mu.g ml-1 for 24 h). 2. Stimulation of protein kinase C with the diacylglycerol analogue, 1-oleoyl-2-acetyl-sn-glycerol (100 .mu.M), also attenuated the inhibition of the sustained calcium current but did not affect the receptor-mediated decrease in rate of current activation. Similarly, okadaic acid (100 nM), a protein phosphatase 1/2A inhibitor, selectively occluded the inhibition of the sustained current. 3. The depression of calcium currents by quinpirole (10 nM) was enhanced following intracellular dialysis with 100 .mu.M cyclic adenosine monophosphate (cyclic AMP, 72.8.+-.9.8% depression), but was not mimicked by the membrane permeant cyclic GMP analogue, Sp-8 -bromoguanosine-3', 5':cyclic monophosphorothioate (100 .mu.M). 4. Inhibition of calcium currents was only partly attenuated by 100 ms depolarizing prepulses to +100mV immediately preceding the test pulse. However, following occlusion of the sustained depression with okadaic acid (100 nM) the residual kinetic slowing was reversed in a voltage-dependent manner ($P<0.05$). 5. Thus pertussis toxin-sensitive G-proteins liberated upon activation of human D(2(short)) dopamine receptors inhibited high-threshold calcium currents in two distinct ways. The decrease in rate of calcium current activation involved a voltage-dependent pathway, whereas the sustained inhibition of calcium current involved, in part, the voltage-resistant phosphorylation by cyclic AMP-dependent protein kinases and subsequent dephosphorylation by protein phosphatases 1/2A.

L74 ANSWER 37 OF 39 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1999-571591 [48] WPIDS
DOC. NO. CPI: C1999-166761
TITLE: Treatment of renal dysfunction using selective beta-isozyme protein kinase C inhibitors, preferably bis-indolyl-maleimide compound.
DERWENT CLASS: B02

INVENTOR(S): GILBERT, R; WAYS, D K
PATENT ASSIGNEE(S): (ELIL) LILLY & CO ELI
COUNTRY COUNT: 86
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9944599	A1	19990910	(199948)*	EN	29
RW: EA GH GM KE LS MW OA SD SL SZ UG ZW					
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW					
EP 951903	A1	19991027	(199950)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
AU 9929047	A	19990920	(200007)		
ZA 9901784	A	20000223	(200016)		25

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9944599	A1	WO 1999-US5447	19990305
EP 951903	A1	EP 1999-200660	19990305
AU 9929047	A	AU 1999-29047	19990305
ZA 9901784	A	ZA 1999-1784	19990305

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9929047	A	Based on	WO 9944599

PRIORITY APPLN. INFO: US 1998-76852 19980305
AB WO 9944599 A UPAB: 19991122
NOVELTY - A method for inhibiting intraglomerular hypertension, glomerulosclerosis or glomerular-intestitial fibrosis, or associated renal dysfunction, involves administration of a **protein kinase C (PKC)** beta - isozyme inhibitor (I).

ACTIVITY - Renal function improvement.

MECHANISM OF ACTION - **PKC** beta -isozyme inhibitor. (I) are especially selective beta -1 or beta -2 isozyme inhibitors. They are thought to reduce intraglomerular pressure and levels of transforming growth factor - beta .

USE - For treating renal dysfunction associated with abnormal glomerular activity, especially renal insufficiency or acute or chronic renal failure.

ADVANTAGE - Treatment with (I) provides a method of controlling certain renal disorders without recourse to renal **dialysis**.

Dwg.0/0

L74 ANSWER 38 OF 39 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2000-225058 [20] WPIDS
DOC. NO. CPI: C2000-068893
TITLE: A method for delivering antisense oligonucleotides to cells using lipid capsules comprising steric barrier lipids.
DERWENT CLASS: A96 B04 D16
INVENTOR(S): ANSELL, S M; CULLIS, P R; HARASYM, T; HOPE, M J; KLIMUK, S K; MOK, W W K; SCHERRER, P; SEMPLE, S C
PATENT ASSIGNEE(S): (ANSE-I) ANSELL S M; (CULL-I) CULLIS P R; (HARA-I) HARASYM T; (HOPE-I) HOPE M J; (KLIM-I) KLIMUK S K; (MOKW-I) MOK W W K; (SCHE-I) SCHERRER P; (SEMP-I) SEMPLE S C
COUNTRY COUNT: 1

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
CA 2271582	A1	19991114	(200020)*	EN	92

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
CA 2271582	A1	CA 1999-2271582	19990513

PRIORITY APPLN. INFO: US 1998-78955 19980514

AB CA 2271582 A UPAB: 20000426

NOVELTY - A method (I) for delivering lipid encapsulated therapeutic agents, especially antisense oligonucleotides, to mammals, is new. The lipid capsule comprises steric barrier lipids that prevent particle aggregation during lipid-nucleic acid formation and exchange out of the particle faster than PEG-Cer20 (polyethylene glycol (PEG) coupled to a ceramide derivative with a 20C acyl chain) ('lipid exchange out of particle' is explained in Patents WO9610391 and WO9610392).

DETAILED DESCRIPTION - A method (I) for the delivery of a lipid encapsulated therapeutic agent to a mammalian cell, comprising:

(1) preparing a lipid encapsulated therapeutic agent particle comprising a therapeutic agent encapsulated within a lipid particle (the lipid particle is formed from a lipid mixture including a steric barrier lipid component that prevents particle aggregation during lipid-nucleic acid particle formation and which exchanges out of the lipid particle at a rate greater than PEG-Cer20); and

(2) administering the particle to a mammal in a number of separate doses separated by intervals of up to 8 weeks.

An INDEPENDENT CLAIM is also included for a method (II) for the prevention or treatment of a disease characterized by aberrant expression of a gene in a mammal, comprising administering a number of doses of a composition comprising lipid-encapsulated nucleic acids at intervals of up to 8 weeks. The lipid-encapsulated nucleic acid particles contain at least 10% by weight (wt%) of nucleic acids which have exclusively phosphodiester linkages.

ACTIVITY - Cytostatic; antiinflammatory; antimicrobial.

MECHANISM OF ACTION - Antisense inhibition of gene expression . The human breast carcinoma line MDA-MB-453 was implanted into a mouse tumor window model according to the method of Wu NZ et al., Increased microvascular permeability contributes to preferential accumulation of Stealth liposomes in tumor tissue, Cancer Research, 53:3765 - 3770 (1993)).

The lipid-antisense formulation consisted of disteroylphosphatidylcholine (DSPC, 25 molar % (mol%)), cholesterol (Chol, 45 mol%), dioleoylphosphatidyldiaminopropane, (DODAP, or AL-1, 20 mol%) and PEG-ceramide (C14 chain length, 10 mol%). For some experiments detailed below, proportions and constituents were altered, but the method of preparation remained the same. Lipids were dissolved in ethanol at 20 mg/ml (PEG-ceramide at 50 mg/ml). Routinely, 1 to 2 mu Ci C-cholesterylhexadecylether was added as a lipid radiolabel. Lipids were mixed in the correct proportions in ethanol to a final concentration of 10 mg in 400 mu l. The lipid mixture was then added dropwise to phosphorothioated antisense (US3: anti-human erb-B-2 GGTGCTCACTGCGGC) dissolved in 300 mM citrate buffer pH 4.0 (600 mu l to make a final volume of 1 ml). The antisense was used at a variety of concentrations, but the optimum concentration for maximum encapsulation efficiency and drug:lipid ratio was determined to be 0.5 mg/ml final. During the addition, the solution became opaque. The DODAP was positively charged at pH 4.0 (pKa = 6.53) and so attracted the negatively charged DNA molecules. The mixture was subjected to five cycles of freezing in liquid nitrogen and thawing at 65 deg. C followed by extrusion through 100 nm filters ten times at 65 deg. C.

After extrusion, two methods can be used for removal of the external antisense. Firstly, the liposomes are diluted 2:1 with citrate (to reduce ethanol content to 20%) then applied to a Bio-Gel A18M 100-200 mesh column equilibrated with HBS (HEPES buffered saline). Alternatively, the liposomes are **dialysed** for 2 hours against citrate to remove ethanol, then overnight against HBS to increase the external pH. The resulting mixture was then applied to a DEAE (undefined) cation exchange column to remove external oligonucleotides. This method was the routine method used for sample preparation for in vivo studies. Antisense concentrations were routinely determined by A260 measurements. Lipid concentrations were determined by scintillation counting after spiking the initial mixture with a known concentration of 3H or 14C cholesteryl hexadecyl ether or by high performance liquid chromatography. Encapsulation efficiency was determined by division of the final drug to lipid ratio by the initial drug to lipid ratio.

When the tumor window had reached a diameter of 2 - 3 mm, treatment with free or TCS (undefined) encapsulated US3 oligonucleotide was initiated. Treatment consisted of a 200 mu l intravenous injection (tail vein) of either free US3 or TCS-encapsulated US3 on a 3 administrations/week schedule and an antisense dose of 10 mg/kg/administration. Tumor size was monitored 3 times a week by microscopy.

It was found that the TCS-encapsulated US3 oligonucleotide was very effective at preventing the growth, or causing extensive size reduction, of the MDA-MB-453 human breast carcinoma in the window model. In contrast, unencapsulated oligonucleotide was ineffective at inhibiting tumor growth.

USE - The method (I) may be used for the delivery of therapeutic agents to mammalian cells. It is especially suitable for delivering nucleic acid molecules, and in particular antisense molecules which may be administered to down regulate the expression of aberrant genes (i.e. method (II)). The aberrant gene may be ICAM-1, c-myc, c-myb, ras, raf, erb-B-2, **PKC**-alpha, IGF-1R, EGFR, VEGF and/or VEG-R-1 (claimed). The method may be used for the treatment of tumors, inflammatory diseases and/or infectious diseases (claimed).

Dwg.0/23

L74 ANSWER 39 OF 39 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1996-426812 [43] WPIDS
CROSS REFERENCE: 1996-426820 [43]
DOC. NO. CPI: C1996-134478
TITLE: Injectable nano-suspension of staurosporin deriv. with poor solubility - esp. N-benzoyl deriv., with polyoxyethylene-polyoxypropylene block copolymer and opt. phospholipid in water-ethanol, used to treat tumours.
DERWENT CLASS: A25 A96 B02 B07
INVENTOR(S): VAN HOOGEVEST, P; WEDER, H G; WEDER, H
PATENT ASSIGNEE(S): (CIBA) CIBA GEIGY AG; (VESI-N) VESIFACT AG; (NOVS) NOVARTIS AG; (NOVS) NOVARTIS-ERFINDUNGEN VERWALTUNGS GMBH; (NOVS) NOVARTIS CORP
COUNTRY COUNT: 26
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
EP 733358	A2	19960925	(199643)*	GE	8
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL PT SE					
NO 9601136	A	19960923	(199647)		
NO 9601137	A	19960923	(199647)		
AU 9648094	A	19961003	(199650)		
AU 9648095	A	19961003	(199650)		
JP 08268893	A	19961015	(199651)		8
JP 08268915	A	19961015	(199651)		8
ZA 9602248	A	19961129	(199702)		19
ZA 9602249	A	19961129	(199702)		17
CA 2172110	A	19960922	(199704)		
CA 2172111	A	19960922	(199704)		

NZ 286207	A	19970424 (199723)	
NZ 286206	A	19970526 (199727)	
HU 9600700	A2	19970228 (199748)	
HU 9600701	A2	19970228 (199748)	
US 5726164	A	19980310 (199817)	8
MX 9601033	A1	19970901 (199850)	
MX 9601032	A1	19981101 (200022)	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 733358	A2	EP 1996-810150	19960312
NO 9601136	A	NO 1996-1136	19960320
NO 9601137	A	NO 1996-1137	19960320
AU 9648094	A	AU 1996-48094	19960315
AU 9648095	A	AU 1996-48095	19960315
JP 08268893	A	JP 1996-63194	19960319
JP 08268915	A	JP 1996-63092	19960319
ZA 9602248	A	ZA 1996-2248	19960320
ZA 9602249	A	ZA 1996-2249	19960320
CA 2172110	A	CA 1996-2172110	19960319
CA 2172111	A	CA 1996-2172111	19960319
NZ 286207	A	NZ 1996-286207	19960319
NZ 286206	A	NZ 1996-286206	19960319
HU 9600700	A2	HU 1996-700	19960320
HU 9600701	A2	HU 1996-701	19960320
US 5726164	A	US 1996-619068	19960320
MX 9601033	A1	MX 1996-1033	19960319
MX 9601032	A1	MX 1996-1032	19960319

PRIORITY APPLN. INFO: CH 1995-804 19950321

AB EP 733358 A UPAB: 20000508

Pharmaceutical compsn. for intravenous admin. of staurosporin deriv. (A) with low solubility in water comprises (A); a polyoxyethylene-polyoxypropylene block copolymer (B); ethanol and water as transport materials; and opt. a phospholipid of formula (I) or its salts, and/or other adjuvants. R1 = 10-20C acyl, R2 = H or 10-20C acyl, R3 = H, 2-trimethylamino-1-ethyl, 2-amino-1-ethyl, 1-4C alkyl, 1-5C alkyl substd. by carboxy, 2-5C hydroxyalkyl (opt. substd. by carboxy), 2-5C alkyl (substd. by carboxy and amino), inositol or glyceryl.

Also claimed is the prepn. of the compsn. by mixing all the components to form a homogenous dispersion; and (1) adding more water and opt. adjuvants, filtering, and opt. **dialysing** to give a clear soln.; or (2) filtering, opt. **dialysing**, drying the dispersion (opt. with addn. of adjuvants) and reconstitution of the dry prepn. to an injectable dispersion.

Also claimed is a nanosuspension contg. (A).

USE - The nanosuspension contg. N-benzoyl-staurosporin is used in tumour therapy (claimed). Staurosporin and its derivs. inhibit **protein kinase C** and other protein kinases and are used to restrict tumour growth, as antiinflammatory agents, as antibiotics, in the treatment of arteriosclerosis and diseases of the cardiovascular system and central nervous system.

ADVANTAGE - The nanosuspension is homogenous and stable, and can be prepared by a simple, conventional mixing process.

Dwg.0/0

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=> d ibib ab 20-29

L74 ANSWER 20 OF 39 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 2
ACCESSION NUMBER: 1999:464780 BIOSIS
DOCUMENT NUMBER: PREV199900464780
TITLE: D-glucose increases the synthesis of tissue-type plasminogen activator (t-PA) in human **peritoneal** mesothelial cells.
AUTHOR(S): Sitter, Thomas (1); Mandl-Weber, Sonja; Woernle, Markus; Haslinger, Bettina; Goedde, Martin; Kooistra, Teake
CORPORATE SOURCE: (1) Medizinische Klinik, Klinikum Innenstadt, Universitaet Muenchen, Ziemssenstrasse 1, D-80336, Muenchen Germany
SOURCE: Thrombosis and Haemostasis, (Sept., 1999) Vol. 82, No. 3, pp. 1171-1176.
ISSN: 0340-6245.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Physical and chemical irritation of the **peritoneum** through glucose-based hyperosmolar **dialysis** solutions results in a nonbacterial serositis with fibrinous exudation. Thereby, human **peritoneal** mesothelial cells (HMC) play an important role in maintaining the balance between the **peritoneal** generation and degradation of fibrin by expressing the fibrinolytic enzyme tissue-type plasminogen activator (t-PA) as well as the specific plasminogen activator inhibitor-1 (PAI-1). In this study, we analyzed the effect of D-glucose and metabolically inert monosaccharides on the synthesis of t-PA and PAI-1 in cultured HMC. Incubation of HMC with D-glucose or the metabolically inert monosaccharides mannitol and L-glucose (5-90 mM) resulted in a time- and concentration-dependent increase in t-PA mRNA expression and antigen secretion without affecting PAI-1 synthesis. A similar effect was evident when HMC were first exposed sequentially to pooled spent **peritoneal dialysis** effluent for up to 4 hours, andsubsequently incubated for 20 hours in control medium. The stimulating effect of high D-glucose on t-PA expression in HMC was prevented by treating the cells with different **protein kinase C (PKC) inhibitors** (Ro 31-8220, Go 6976), but could not be mimicked by the PKC-activating phorbol ester PMA, indicating that this effect of high glucose is dependent on PKC activity, but not mediated through **PKC** activation. Also, using specific inhibitors (PD 98059, SB 203580) and activators (PMA, anisomycin, IL-1alpha) of the major routes of the mitogen-activated protein kinases (MAPKs) cascade, we found no evidence for a role of this cascade in regulating t-PA expression in HMC. We conclude that hyperosmolarity induces t-PA (but not PAI-1) in HMC via a regulatory mechanism that requires active PKC, but that does not involve a major pathway in the MAPK cascade.

L74 ANSWER 21 OF 39 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 3

ACCESSION NUMBER: 1998:519057 BIOSIS
DOCUMENT NUMBER: PREV199800519057
TITLE: High glucose increases prostaglandin E2 synthesis in human **peritoneal** mesothelial cells: Role of hyperosmolarity.
AUTHOR(S): Sitter, Thomas (1); Haslinger, Bettina; Mandl, Sonja; Fricke, Harald; Held, Eckhard; Sellmayer, Alois
CORPORATE SOURCE: (1) Med. Klinik, Klinikum Innenstadt Univ. Muenchen, Ziemssenstrasse 1, D-80336 Munich Germany
SOURCE: Journal of the American Society of Nephrology, (Nov., 1998) Vol. 9, No. 11, pp. 2005-2012.
ISSN: 1046-6673.
DOCUMENT TYPE: Article
LANGUAGE: English

1,2,16,17,23

AB **Peritoneal** mesothelial cells are considered the predominant source of **peritoneal** prostanoid formation because they represent the largest resident cell population in the **peritoneal** cavity. The present study was designed to evaluate the effect of D-glucose, which is widely used in commercially available **peritoneal dialysis** fluids as an osmotic compound, on the synthesis of prostaglandins in cultured human mesothelial cells (HMC). Analysis of eicosanoid synthesis in HMC by reversed-phase HPLC revealed that 6-keto-PGF1alpha, the spontaneous hydrolysis product of prostacyclin (PGI2), and prostaglandin E2 (PGE2) were the main eicosanoids produced. Addition of D-glucose resulted in a time- and concentration-dependent (30 to 120 mM) increase in PGE2 production in HMC (24 h, 90 mM: 3.9 +- 0.5 ng/105 cells versus 2.3 +- 0.3 in untreated cells; $P < 0.05$). Mannitol (90 mM) or L-glucose (90 mM), nonmetabolizable osmotic compounds, also led to a significant ($P < 0.05$) but less intense increase in PGE2 synthesis (3.3 +- 0.4 and 3.2 +- 0.5 ng/105 cells, respectively). Increased PGE2 synthesis was completely blunted by coincubation with the specific **protein kinase C** (**PKC**) **inhibitor** Ro 31-8220 or downregulation of PKC activity by preincubation with phorbol myristate acetate for 16 h. Furthermore, coincubation with PD 98059, an inhibitor of the mitogen-activated protein kinase/extracellular signal-regulated kinase pathway, also inhibited increased PGE2 synthesis by D-glucose or mannitol. In contrast, the iso-osmolar glucose polymer icodextrin, which is used as an alternative to D-glucose in **peritoneal dialysis** solutions, had no effect on PGE2 synthesis. These data indicate that D-glucose and metabolically inert sugars increase PGE2 synthesis in HMC at least in part by hyperosmolarity and that this effect requires activation of PKC and the mitogen-activated protein kinase/extracellular signal-regulated kinase pathway of intracellular signaling.

L74 ANSWER 22 OF 39 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 2000:151816 BIOSIS
DOCUMENT NUMBER: PREV200000151816
TITLE: Protein kinase C enhances the rapidly activating delayed rectifier potassium current, IKr, through a reduction in C-type inactivation in guinea-pig ventricular myocytes.
AUTHOR(S): Heath, B. M. (1); Terrar, D. A.
CORPORATE SOURCE: (1) University Department of Pharmacology, Mansfield Road, Oxford, OX1 3QT UK
SOURCE: Journal of Physiology (Cambridge)., (Feb 1, 2000) Vol. 522, No. 3, pp. 391-402.
ISSN: 0022-3751.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB 1. The rapidly activating delayed rectifier potassium current, IKr, was studied in guinea-pig ventricular myocytes in the presence of thiopentone, which blocks the more slowly activating component of the delayed rectifier potassium current, IKs, and using whole cell perforated patch clamp or switched voltage clamp with sharp electrodes to minimise intracellular **dialysis**. 2. Activation of protein kinase A (PKA) by isoprenaline

or forskolin caused an increase in IKr tail currents. Following a 300 ms depolarising step to +20 mV, mean tail current amplitude was increased 47 +- 12% by isoprenaline, and 73 +- 13% by forskolin. No increase in IKr was observed when IKr was studied using whole cell ruptured patch clamp and there was no change in the reversal potential of IKr in the presence of isoprenaline. 3. The rectification of the current sensitive to E4031, a selective IKr blocker, was markedly reduced in the presence of isoprenaline and the region of negative slope was absent. This is consistent with a reduction in the inactivation of IKr and was supported by the finding that IKr, in the presence of isoprenaline, was somewhat less sensitive to block. E4031 (5 muM) blocked only 81 +- 5% of IKr in the presence of isoprenaline compared to 100 +- 0% in control. 4. The forskolin- and isoprenaline-induced increases in IKr were inhibited by staurosporine and by the selective protein kinase C (PKC) inhibitor **bisindolylmaleimide** I. Direct activation of PKC by phorbol dibutyrate increased IKr tail currents by 24 +- 5%. Both the isoprenaline-and forskolin-induced increases in IKr were inhibited when calcium entry was reduced by block of ICa with nifedipine or when myocytes were pre-incubated in BAPTA-AM. 5. The selective PKA inhibitor KT5720 prevented the isoprenaline-induced increase in IKr only when the increase in ICa was also suppressed. 6. These data show a novel mechanism of regulation of IKr by PKC and this kinase was activated by beta-adrenoceptor stimulation. IKr seems to be enhanced through a reduction in the C-type inactivation which underlies the rectification of the channel and such a mechanism may occur in other channels with this type of inactivation.

L74 ANSWER 23 OF 39 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 2000:524483 BIOSIS
DOCUMENT NUMBER: PREV200000524483
TITLE: D-glucose increases the synthesis of tissue-type plasminogen activator (t-PA) in human **peritoneal** mesothelial cells.
AUTHOR(S): Sitter, T. (1); Mandl-Weber, S.; Woernle, M.; Haslinger, B.; Goedde, M.; Kooistra, T.
CORPORATE SOURCE: (1) Klinikum Innenstadt, Ludwig-Maximilians-Universitaet, Munich Germany
SOURCE: Kidney & Blood Pressure Research, (1999) Vol. 22, No. 4-6, pp. 328-329. print.
Meeting Info.: Joint Scientific Meeting of the Society for Nephrology and the German Working Group for Clinical Nephrology Freiburg, Germany September 18-21, 1999
ISSN: 1420-4096.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L74 ANSWER 24 OF 39 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1999:311749 BIOSIS
DOCUMENT NUMBER: PREV199900311749
TITLE: Regulation of L-type Ca2+ channels in rabbit portal vein by G protein alphas and betagamma subunits.
AUTHOR(S): Zhong, Juming; Dessauer, Carmen W.; Keef, Kathleen D.; Hume, Joseph R. (1)
CORPORATE SOURCE: (1) Department of Physiology and Cell Biology/351, University of Nevada School of Medicine, Reno, NV, 89557 USA
SOURCE: Journal of Physiology (Cambridge), (May 15, 1999) Vol. 517, No. 1, pp. 109-120.
ISSN: 0022-3751.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB 1. The effect of purified G protein subunits alphas and betagamma on L-type Ca2+ channels in vascular smooth muscle and the possible pathways involved were investigated using freshly isolated smooth muscle cells from

rabbit portal vein and the whole-cell patch clamp technique. 2. Cells **dialysed** with either Galphas or Gbetagamma exhibited significant increases in peak Ba2+ current (IBa) density (148% and 131%, respectively) compared with control cells. The combination of Galphas and Gbetagammafurther increased peak IBa density (181%). Inactive Galphas and Gbetagamma did not have any effect on Ca2+ channels. 3. The stimulatory effect of Galphas on peak IBa was entirely abolished by the protein kinase A inhibitor Rp-8-Br-cAMPS, or the adenylyl cyclase inhibitor SQ 22536. On the other hand, the stimulatory response of Ca2+ channels to Gbetagamma was not affected by the protein kinase A inhibitors Rp-8-Br-cAMPS and KT 5720, or by the Ca2+-dependent protein kinase C inhibitor **bisindolylmaleimide** 1, but was completely blocked by the protein kinase C inhibitor calphostin C. Pretreatment of cells with phorbol 12-myristate 13-acetate for over 18 h prevented the stimulatory effect of Gbetagamma on peak IBa. In addition, acute application of phorbol 12,13-dibutyrate enhanced peak IBa density in control cells, which could be entirely blocked by calphostin C. 4. These data indicate that enhancement of Ba2+ currents by Galphas and Gbetagamma can be attributed to increased activity of protein kinase A and protein kinase C, respectively. No direct membrane-delimited pathway for Ca2+ channel regulation by activated Gs proteins could be detected in vascular smooth muscle cells.

L74 ANSWER 25 OF 39 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1998:387791 BIOSIS
DOCUMENT NUMBER: PREV199800387791
TITLE: PKC regulation of cardiac CFTR Cl- channel function in guinea pig ventricular myocytes.
AUTHOR(S): Middleton, Lisa M.; Harvey, Robert D. (1)
CORPORATE SOURCE: (1) Dep. Physiol. Biophys., Case Western Res. Univ., 2109 Adelbert Road, Cleveland, OH 44106-4970 USA
SOURCE: American Journal of Physiology, (July, 1998) Vol. 275, No. 1 PART1, pp. C293-C302.
ISSN: 0002-9513.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The role of protein kinase C (PKC) in regulating the protein kinase A (PKA)-activated Cl- current conducted by the cardiac isoform of the cystic fibrosis transmembrane conductance regulator (cCFTR) was studied in guinea pig ventricular myocytes using the whole cell patch-clamp technique. Although stimulation of endogenous PKC with phorbol 12,13-dibutyrate (PDBu) alone did not activate this Cl- current, even when intracellular **dialysis** was limited with the perforated patch-clamp technique, activation of PKC did elicit a significant response in the presence of PKA-dependent activation of the current by the beta-adrenergic receptor agonist isoproterenol. PDBu increased the magnitude of the Cl- conductance activated by a supramaximally stimulating concentration of isoproterenol by 21 +- 3.3% (n = 9) when added after isoproterenol and by 36 +- 16% (n = 14) when introduced before isoproterenol. 4alpha-Phorbol 12,13-didecanoate, a phorbol ester that does not activate PKC, did not mimic these effects. Preexposure to chelerythrine or **bisindolylmaleimide**, two highly selective inhibitors of PKC, significantly reduced the magnitude of the isoproterenol-activated Cl- current by 79 +- 7.7% (n = 11) and 52 +- 10% (n = 8), respectively. Our results suggest that although acute activation of endogenous PKC alone does not significantly regulate cCFTR Cl- channel activity in native myocytes, it does potentiate PKA-dependent responses, perhaps most dramatically demonstrated by basal PKC activity, which may play a pivotal role in modulating the function of these channels.

L74 ANSWER 26 OF 39 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1996:151353 BIOSIS
DOCUMENT NUMBER: PREV199698723488
TITLE: Protein kinase C activates ATP-sensitive K+ current in human and rabbit ventricular myocytes.
AUTHOR(S): Hu, Keli; Duan, Dayue; Li, Gui-Rong; Nattel, Stanley (1)

CORPORATE SOURCE: (1) Montreal Heart Inst., 5000 Belanger St. E, Montreal, PQ H1T 1C8 Canada
SOURCE: Circulation Research, (1996) Vol. 78, No. 3, pp. 492-498. ISSN: 0009-7330.
DOCUMENT TYPE: Article
LANGUAGE: English

AB Mediators involved in ischemic preconditioning, such as adenosine and norepinephrine, can activate protein kinase C (PKC), and a variety of observations suggest that both PKC and ATP-sensitive K+ current (I-KATP) play essential roles in ischemic preconditioning. PKC is therefore a candidate to link receptor binding to I-KATP activation, but it has not been shown whether and how PKC can activate I-KATP in the heart. The present study was designed to determine whether PKC can activate I-KATP in rabbit and human ventricular myocytes. Under conditions designed to minimize Na+ and Ca-2+ currents, **dialysis** of rabbit ventricular myocytes with pipette solutions containing reduced (ATP) elicited I-KATP, with a 50% effective concentration (EC-50) of 260 mu-mol/L. In cells that failed to show I-KATP under control conditions, superfusion with 1 mu-mol/L phorbol 12,13-didecanoate (PDD) elicited I-KATP in a fashion that depended on pipette (ATP), with an (ATP) EC-50 of 601 mu-mol/L. PDD-induced I-KATP activation was concentration dependent, with an EC-50 of 7.1 nmol/L. The highly selective PKC inhibitor **bisindolylmaleimide** totally prevented I-KATP activation by PDD, and in blinded experiments, 1 mu-mol/L PDD elicited I-KATP in eight of nine cells, whereas its non-PKC-stimulating analogue 4-alpha-PDD failed to elicit I-KATP in any of the five cells tested (P=.003). Similar experiments were conducted in human ventricular myocytes and showed that 0.1 mu-mol/L PDD elicited I-KATP at pipette (ATP) of 100 and 400 mu-mol/L (five of five cells at each concentration) but not at 1 mmol/L (ATP) (none of five cells). We conclude that PKC activates I-KATP in rabbit and human ventricular myocytes by reducing channel sensitivity to intracellular ATP. This finding has potentially important implications for understanding the mechanisms of ischemic preconditioning.

L74 ANSWER 27 OF 39 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1995:450633 BIOSIS
DOCUMENT NUMBER: PREV199598464933
TITLE: Depletion-activated calcium current is inhibited by protein kinase in RBL-2H3 cells.
AUTHOR(S): Parekh, Anant B.; Penner, Reinhold
CORPORATE SOURCE: Dep. Membrane Biophysics, Max Planck Inst. Biophsyical Chem., Am Fassberg, D-37707 Goettingen Germany
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1995) Vol. 92, No. 17, pp. 7907-7911. ISSN: 0027-8424.
DOCUMENT TYPE: Article
LANGUAGE: English

AB Whole-cell patch-clamp recordings and single-cell Ca-2+ measurements were used to study the control of Ca-2+ entry through the Ca-2+ release-activated Ca-2+ influx pathway (I-CRAC) in rat basophilic leukemia cells. When intracellular inositol 1,4,5-trisphosphate (InsP-3)-sensitive stores were depleted by **dialyzing** cells with high concentrations of InsP-3, I-CRAC inactivated only slightly in the absence of ATP. Inclusion of ATP accelerated inactivation 2-fold. The inactivation was increased further by the ATP analogue adenosine 5'-(gamma-thio)triphosphate, which is readily used by protein kinases, but not by 5'-adenylyl imidodiphosphate, another ATP analogue that is not used by kinases. Neither cyclic nucleotides nor inhibition of calmodulin or tyrosine kinase prevented the inactivation. Staurosporine and **bisindolylmaleimide**, protein kinase C inhibitors, reduced inactivation of I-CRAC, whereas phorbol ester accelerated inactivation of the current. These results demonstrate that a protein kinase-mediated phosphorylation, probably through protein kinase C, inactivates I-CRAC. Activation of the adenosine receptor (A-3 type) in RBL cells did not evoke much Ca-2+ influx or systematic activation of I-CRAC. After protein kinase

C was blocked, however, large I-CRAC was observed in all cells and this was accompanied by large Ca-2+ influx. The ability of a receptor to evoke Ca-2+ entry is determined, at least in part, by protein kinase C. Antigen stimulation, which triggers secretion through a process that requires Ca-2+ influx, activated I-CRAC. The regulation of I-CRAC by protein kinase will therefore have important consequences on cell functioning.

L74 ANSWER 28 OF 39 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1995:112746 BIOSIS
DOCUMENT NUMBER: PREV199598127046
TITLE: Cortisol Inhibition of Calcium Currents in Guinea Pig Hippocampal CA1 Neurons via G-Protein-coupled Activation of Protein Kinase C.
AUTHOR(S): Ffrench-Mullen, Jariath M. H.
CORPORATE SOURCE: Dep. Pharmacol., Zeneca Pharmaceuticals Group, Zeneca Inc., Wilmington, DE 19897 USA
SOURCE: Journal of Neuroscience, (1995) Vol. 15, No. 1 PART 2, pp. 903-911.
ISSN: 0270-6474.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The inhibition of voltage-activated Ca-2+ channel currents by cortisol (hydrocortisone), the principal glucocorticoid in man and guinea pig, was examined in freshly dissociated pyramidal neurons from the adult guinea pig hippocampal CA1 region using whole-cell voltage-clamp recordings. Steady-state inhibition by cortisol of the peak Ca-2+ channel current evoked by depolarization from -80 to -10 mV increased in a concentration-dependent fashion, with a maximal inhibition of 63 +- 4% of the total current at 100 mu-M. Cortisone had a maximal 17 +- 2% inhibition at 10 mu-M. Corticosterone and the metabolite allotetrahydrodeoxycorticosterone exhibited a plateau of inhibition of around 15% and 25%, respectively, between 10 pM and 100 nM; both compounds continued to inhibit at concentrations gt 10-7 M. Analysis of tail currents at -80 mV showed that cortisol and corticosterone had no effect on the voltage-dependent activation or deactivation of the Ca-2+ channel current. However, cortisol slowed the activation of the current. Cortisol inhibited both the N-type or omega-conotoxin (CgTX)-sensitive,and the L-type or nifedipine (NIF)-sensitive Ca-2+ channel current but had no effect on the CgTX/NIF-insensitive Ca-2+ channel current. In neurons isolated from pertussis toxin (PTX)-treated animals, the cortisol inhibition was significantly diminished. Intracellular **dialysis** with GDP-beta-S (500 mu-M) or with the specific inhibitors of protein kinase C (PKC), the pseudosubstrate PKC inhibitor (PKCI 19-31) (2 mu-M) and **bisindolylmaleimide** (BIS) (1 mu-M) significantly diminished the cortisol inhibition of the Ca-2+ channel current. The specific inhibitor of cAMP-dependent protein kinase (PKA) inhibitor, Rp-cAMPS (100 mu-M) had no effect. These results demonstrate that cortisol is a potent modulator of both the CgTX- and NIF-sensitive Ca-2+ channel current but not the CgTX/NIF-insensitive current. This inhibition is via a PTX-sensitive G-protein-coupled mechanism associated with the activation of PKC.

L74 ANSWER 29 OF 39 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1994:229207 BIOSIS
DOCUMENT NUMBER: PREV199497242207
TITLE: Neurosteroids modulate calcium currents in hippocampal CA1 neurons via a pertussis toxin-sensitive G-protein-coupled mechanism.
AUTHOR(S): Ffrench-Mullen, Jarlath M. H. (1); Danks, Petra; Spence, Katherine T.
CORPORATE SOURCE: (1) Dep. Pharmacol., Zeneca Pharmaceuticals Group, Zeneca Inc., Wilmington, DE 19897 USA
SOURCE: Journal of Neuroscience, (1994) Vol. 14, No. 4, pp. 1963-1977.
ISSN: 0270-6474.
DOCUMENT TYPE: Article

LANGUAGE: English

AB The inhibition of Ca-2+ channel currents by endogenous brain steroids was examined in freshly dissociated pyramidal neurons from the adult guinea pig hippocampal CA1 region. The steady-state inhibition of the peak Ca-2+ channel current evoked by depolarizing steps from -80 to -10 mV occurred in a concentration-dependent manner with the following IC-50 values: pregnenolone sulfate (PES), 11 nM; pregnenolone (PE), 130 nM; and allotetrahydrocorticosterone (THCC), 298 nM. THCC, PE, and PES depressed a fraction of the Ca-2+ channel current with a maximal inhibition of 60% of the total current. However, substitution of an acetate group for the concomitant extracellular perfusion of PES showed normal inhibitory activity, suggesting that the steroid binding site can only be accessed extracellularly. Analysis of tail currents at -80 mV demonstrated that THCC and PES slowed the rate of Ca-2+ current activation and deactivation with no change in the voltage dependence of activation. Inhibition of the Ca-2+ channel current by THCC and PES was voltage dependent. THCC primarily inhibits the omega-conotoxin (CgTX)sensitive or N-type Ca-2+ channel current. PE was nonselective in inhibiting both the CgTX- and the nifedipine (NIF)sensitive Ca-2+ channel current. These neurosteroids had no effect on the CgTX/NIF-insensitive current. In neurons isolated from pertussis toxin (PTX)-treated animals by chronic intracerebroventricular infusion (1000 ng/ 24 hr for 48 hr), the Ca-2+ channel current inhibition by PES, PE, and THCC was significantly diminished. Intracellular **dialysis** with GDP-beta-S (500 mu-M) also significantly diminished the neurosteroid inhibition of the Ca-2+ channel current. Intracellular **dialysis** with the general kinase inhibitors H-7 (100 mu-M), staurosporine (400 nM), and a 20 amino acid protein kinase inhibitor (1 mu-M) also significantly prevented the THCC and PES inhibition of the Ca-2+ channel current. Intracellular **dialysis** with the more specific inhibitors of protein kinase C (PKC), the pseudosubstrate inhibitor (PKCI 19-36) (1-2 mu-M) and **bisindolylmaleimide** (1 mu-M) significantly diminished the THCC and PE inhibition of the Ca-2+ channel current. Rp-cAMPS (100 mu-M), a specific inhibitor of cAMP-dependent protein kinase (PKA), had no effect on the THCC and PE inhibition of the Ca-2+ current. These results demonstrate that neurosteroids, acting at a membrane receptor site, are potent modulators of either the CgTX- and/or the NIF-sensitive Ca-2+ channel current but not the CgTX/NIF-insensitive current. Furthermore, the Ca-2+ channel current inhibition is via a PTX-sensitive G-protein-coupled mechanism associated with the activation of PKC. Thus, inhibition of Ca-2+ channel currents by neurosteroids may participate in the regulation of synaptic processes such as modulation of neuronal activity and/or neurotransmitter release-associated mechanisms via a G-protein mechanism(s).